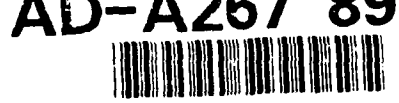

TECHNICAL REPORT

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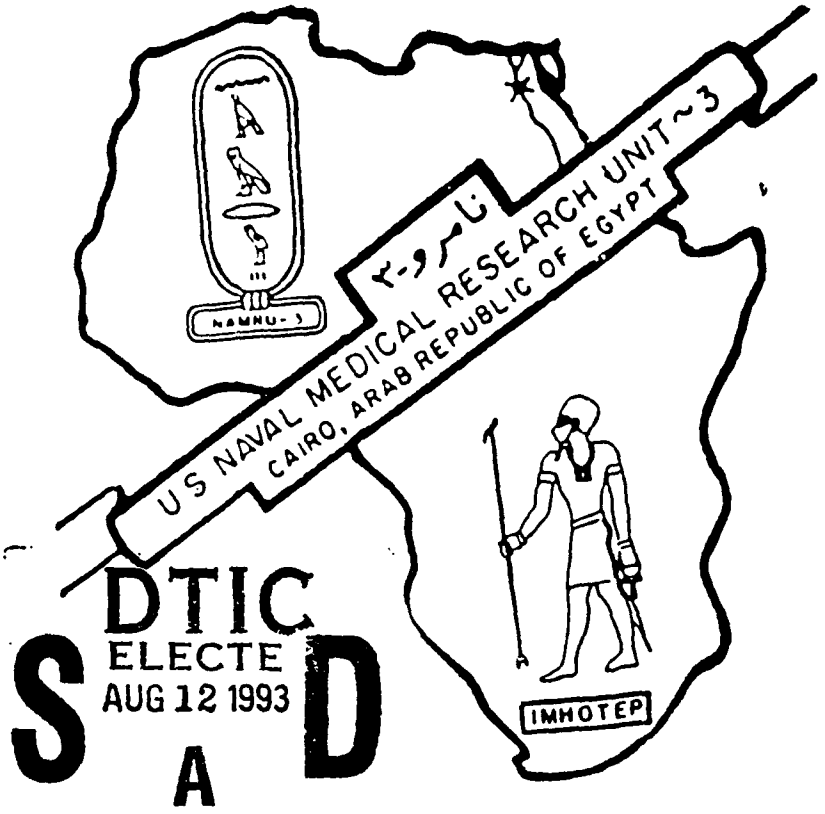

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R.R. Abu-Elyazeed, MD. PhD.

I.K. Podgore, D.O.

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A randomized double-blind trial was conducted in Fayoum, Egypt, to assess the efficacy of twice-weekly application of 1% niclosamide lotion to prevent S. haematobium re-infection. Farmers aged 18-40 years were treated by praziquantel to cure their S. haematobium infection. Subjects were randomly assigned to receive niclosamide or placebo lotion which was self-applied, under observation, to limbs, neck and torso twice weekly for 26 weeks. Subjects were exposed to schistosomal infested water during routine irrigation activities from April to October 1992. Urine specimens were evaluated by te Nucleopore filtration method monthly during and 4 month following the lotion application period. Those included in the statistical analysis were free from S. haematobium ova in urine in the first 4 months after the start of lotion application. Three hundred and fifty subjects met the inclusion criteria and completed the trial, 169 (48.3%) in the niclosamide group and 181 (51.7%) in the placebo group. The subjects assigned to the niclosamide group were comparable to those in the placebo group in age (27.2 vs 27.8 years), total water contact (101.9 vs 109.0 hours), reported 98-100% lotion application compliance (93.5% vs 90.6%) and reported no water contact involving whole body (94.7% vs 96.7%). The re-infection rate of S. haematobium based on the presence of ova in urine up to 12 weeks after cessation of lotion application was 30.8% in the niclosamide and 28.2% in the placebo group. The re-infection rates up to 16 weeks were 37.3% and 32.0% in the niclosamide and placebo groups, respectively. Niclosamide lotion applied to the limbs and truck twice weekly did not prevent S. haematobium re-infection. Previous studies in monkeys with both S. haematobium and S. mansoni and in humans with S. mansoni showed that 1% niclosamide was effective in preventing re-infection. A more rigorous application regimen may be indicated.

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By

R.R. Abu-Elyazeed, MD. PhD.

J.K. Podgore, D.O.

United States Naval Medical Research Unit No.3
Cairo, Egypt
FPO, AE 09835-0007
FAX 011-202-282-2039

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Summary

A randomized double-blind trial was conducted in Fayoum, Egypt, to assess the efficacy of twice-weekly application of 1% niclosamide lotion to prevent S.haematobium re-infection. Farmers aged 18-40 years were treated by praziquantel to cure their S. haematobium infection. Subjects were randomly assigned to receive niclosamide or placebo lotion which was self-applied, under observation, to limbs, neck and torso twice weekly for 26 weeks. Subjects were exposed to schistosomal infested water during routine irrigation activities from April to October 1992. Urine specimens were evaluated by the Nuclepore filtration method monthly during and 4 months following the lotion application period. Those included in the statistical analysis were free from S. haematobium ova in urine in the first 4 months after the start of lotion application. Three hundred and fifty subjects met the inclusion criteria and completed the trial, 169 (48.3%) in the niclosamide group and 181 (51.7%) in the placebo group. The subjects assigned to the niclosamide group were comparable to those in the placebo group in age (27.2 vs 27.8 years), total water contact (101.9 vs 109.0 hours), reported 98-100% lotion application compliance (93.5% vs 90.6%) and reported no water contact involving whole body (94.7% vs 96.7%). The re-infection rate of S. haematobium based on the presence of ova in urine up to 12 weeks after cessation of lotion application was 30.8% in the niclosamide and 28.2%

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INTRODUCTION AND BACKGROUND

A. INTRODUCTION

Schistosomiasis is one of the major public health problems of tropical and sub-tropical developing regions. The disease is endemic in 74 countries including extensive areas in Africa, Asia, the Middle East, South America and the Caribbean.[1] Over 200 million people are currently infected and with the recent expansion in water development resources in the developing world the number of people at risk is expanding.[2] Agricultural workers and their families in endemic areas that have continuous exposure to schistosomal cercarial infested water through farm labor, washing, bathing, and water recreation have great difficulty and perhaps no practical means of remaining free of recurrent infection. Tourists and urban dwellers that come in contact with these endemic areas are also susceptible to schistosomal infection. During the landing of American military personnel at Leyte in the Philippines during World War II approximately 80% of the soldiers of some units in the landing force contracted acute Katayama fever (acute schistosomiasis).

B. LIFE CYCLE

Schistosomiasis is a water borne disease. The principal reservoir is man, and of the five major species which infect man, two (Schistosoma mansoni and Schistosoma haematobium) are found in Egypt.

Adult parasites (worms) live in the venules that surround the urinary bladder (S. haematobium). Ten to twelve weeks after infection of the host organism, the female worm begins laying over 300 eggs per day. Approximately one third of the eggs pass out in the urine of infected individuals . The rest of the remaining eggs are trapped either in the bladder walls or are swept back by the blood flow to become lodged in ectopic sites such as the liver, spleen and other tissues. It is the accumulation of eggs in the body tissues that causes the morbidity associated with schistosomiasis.

After passing from the body, free-swimming ciliated larvae, called miracidia, quickly hatch from the eggs. The miracidium must find a suitable snail within 6 hours or die. The fresh water snail, predominantly from the genus Bulinus, is the intermediate host for S. haematobium in Egypt. In the snail, the miracidium transforms into two sporocyst stages. Reproduction occurs only in the (snail) intermediate host. After four weeks, the snail releases into the water a free-swimming larval form of the organism, known as the cercaria.

The cercariae attach to the host organism (man), secrete proteolytic enzymes and penetrate directly through the skin. Once inside the body, the development of the worm begins and the life cycle begins anew.

Acute schistosomiasis occurs after non-infected individuals have non-protected contact with schistosomal cercarial infested waters. The exposure and infection may

occur after just a few minutes of contact with cercarial infested waters. The severe disabling condition known as Katayama Fever, which can occur 4 to 6 weeks after initial penetration of S. mansoni cercarial larvae through the skin of a previously uninfected human, has not been reported for S. haematobium. However, the morbidity associated with S. haematobium infection is severe, as a high degree of incidence of urinary bladder carcinoma has been associated with infection by this species. Currently, with the exception of avoiding potentially infested schistosomal cercarial waters or wearing suitable protective boots, gloves and non-penetrable clothing, there is no effective means of preventing schistosomiasis in people that must make contact with infested waters.

C. NICLOSAMIDE

Niclosamide (WR 046234, 2',5-dichloro-4'-nitrosalicylanilide) has been used for prophylaxis and therapy throughout the world for the past 30 years.[3] It has been used as therapy for cestode infections in man since 1960 with no reports of serious adverse reactions.[4] It is prescribed orally at a dose of 2 grams daily for 7 days for treatment of human tapeworm infection. It is only partially absorbed from the intestinal tract and is eliminated rapidly without adverse effects on liver, kidney or hematological systems.[3-5] The absorbed fraction is eliminated by the kidneys. It is also used as a schistosomicide and molluscicide. It was tested extensively in Egypt as a molluscicide under the trade

name "Mollutox".[6] In the form of a 70% dispersible powder "Bayluscide", it has been applied in spray form and used in Egypt and the rest of Africa to kill snails, snail eggs, and schistosome cercariae. The biochemical activity of niclosamide on cestodes is associated with its ability to inhibit oxidative phosphorylation in the mitochondria of these parasites. It also affects the respiration and carbohydrate metabolism of miracidia.[3] Its poor topical and systemic absorption in humans contributes to its safety and extremely low toxicity.

A topical lotion containing 1% niclosamide has been tested and shown to be effective in preventing schistosome cercarial penetration of the skin of hamsters and non-human primates (Cebus apella).[7-9] No gross dermatological effects were noted in any of the animals treated with the lotion. No skin irritation has been noted in humans during skin contact of niclosamide molluscicide preparations and no sensitizing effect was seen in subjects with photoallergic reactions to tribromosalicylanilide.[10] Skin reactions were occasionally seen with applications of a 25% emulsion preparation of niclosamide which were proven to be due to other ingredients and not niclosamide itself.[11] In humans, a randomized, double blind, placebo controlled field trial of a topical antipenetrant lotion 1% niclosamide applied daily to the upper and lower limbs of farmers occupationally exposed to S. mansoni cercarial infested water was conducted in the Nile Delta in Egypt in 1991. A total of 194 rice farmers applied study

medication daily for 5 months.[12] There were neither skin rashes nor other adverse reactions noted during that study. The schistosomal reinfection rate was lower in the niclosamide group (55%) compared to the placebo group (71%), ($P < .02$).

D. PROPHYLAXIS AGAINST SCHISTOSOMIASIS

There is no known chemoprophylaxis against schistosomiasis. The only prophylaxis, which is the accepted medical approach to the prevention of schistosomiasis, is the elimination of all direct skin contact with potentially infested water by strict avoidance or through the use of protective boots, gloves, and clothing impenetrable to schistosomal cercariae. The potential protective option of a topical preparation that can be self-applied and will prevent schistosomiasis by inhibiting cercarial penetration has great practical military significance. It would offer a readily accessible form of portable and inexpensive protection in anticipated or potential threat areas where contact with infested water cannot be avoided.

E. CHEMOTHERAPY FOR SCHISTOSOMIASIS

In the past ten years, treatment of chronic schistosomiasis has been greatly facilitated by the availability of praziquantel, a proven effective and minimally toxic chemotherapeutic agent for S. mansoni, S. haematobium, as well as S. japonicum. A single dose of praziquantel, at 30 to 60 mg per kg body weight given orally clears feces and urine of viable schistosomal eggs and gives cure rates ranging from 63 to 100%.[13]

Praziquantel toxicity is limited to minor transient side effects including occasional nausea, vomiting, and abdominal cramping. The problem of the potential development of resistance to the various schistosomal drugs is being monitored and its emergence is a likelihood.[14,15]

F. REINFECTION RATES AFTER CHEMOTHERAPY

A clinical cure for schistosomiasis in the study is defined as the cessation of passing viable schistosome eggs following treatment. If a person never stops passing eggs after treatment, even though the number of eggs is greatly reduced, that condition is considered a treatment failure. Reinfection is defined as the presence of viable schistosome eggs detected in urine at 10 weeks or more after successful therapy. Successful treatment is defined as the absence of viable schistosome eggs detected in a minimum of 3 consecutive urine examinations 5-10 weeks after therapy. This definition of successful treatment has been selected since Schistosoma haematobium cercariae require at least 10 weeks after they penetrate the skin to mature into egg-producing adults.

Statement of Purpose:

The purpose of this study was to determine if a 1% niclosamide skin lotion self-

applied twice weekly to the upper and lower limbs, neck and torso was safe and protective against Schistosoma hematobium cercarial re-infection in Egyptian agricultural workers who had recently been treated by the Egyptian Ministry of Health for schistosomiasis. If the topical antipenetrant lotion was safe, effective and practical, it could be used where the threat of short term, high level cercarial contact is anticipated. For example, it might be used during short term farm irrigation projects and by tourists and military personnel anticipating potential exposure to heavily infested cercarial waters during excursions and field operations.

Materials and Methods:

Study Design:

This study was a prospective, randomized, double blind, placebo controlled field trial.

Study Area:

The study was conducted in the Fayoum Governorate, Arab Republic of Egypt. Subjects were selected from the populations of the farming villages in the Fayoum. The Fayoum was selected because of a historically documented prevalence of S. haematobium (greater than 99% of the schistosomiasis cases are S.haematobium). This location is also relatively accessible from the Naval Medical Research Unit, No.3 (NAMRU-3) in Cairo. The total population of Fayoum is approximately 1.7 million.

The Fayoum Governorate is an oasis located in the Sahara Desert approximately 100 km. southwest of Cairo. It is the largest oasis in Egypt. Roads in and out of Fayoum are fair to good; one paved road connects the capital of the governorate with Cairo and most of the villages are linked by hard-packed roads.

The major occupation in Fayoum is agriculture. Wheat, corn, sorghum and vegetables are grown in irrigated fields. Water is fed to the region both directly from the Nile through the Joseph Canal, and through natural springs. Within the governorate, water is distributed through a series of canals, and from there it is pumped into the fields to irrigate the crops. The canal water is heavily infested with fresh water snails harboring schistosomiasis.

Four villages: Mousharak Bahary, Mousharak Qebly, Kahk and Batn Ihrit were selected due to the high prevalence of endemic Schistosoma haematobium infection detected during recent Egyptian Ministry of Health surveys. The male inhabitants of these villages were primarily farmers and did not differ greatly in respect to their living style and activities.

Study Population:

A. Sample size

The minimum level of protection from re-infection afforded by 1% niclosamide that we selected as acceptable was 70%. The re-infection rate in the control group was

estimated at 15% during the 6 months occupational exposure period. The re-infection rate in the treatment group that would be expected if the niclosamide lotion is effective is 4.5% (.30 x 15%). An estimation of a minimum 192 subjects in each group was required in order to have an 80% chance of detecting this difference (power) when the significance alpha level is 0.05, two-tail test.[16]

Six hundred male Egyptian farmers were enrolled in this study. This number was selected to accommodate for possible loss of subjects due to drop outs, failure of praziquantel treatment or other disqualifying factors. A list of farmers recently treated and determined to be free of schistosomiasis was provided to the NAMRU-3 investigators by the Egyptian Ministry of Health from which volunteers were solicited for this study.

B. Inclusion Criteria

The inclusion criteria for the entry to the lotion application phase of the study were:

(1) Absence of schistosomiasis infection as determined by the 3 consecutive daily urine analysis at the time the informed consent is obtained

(2) Anticipate exposure to schistosomal infested water during the irrigation season

(3) Agree to apply the lotion twice a week to upper and lower limbs, neck and torso for 6 months

(4) Willingness to undergo regular monitoring for adherence to the protocol

(5) Agree to avoid total body contact with potentially infested water for the duration of the study

(6) Agree to report daily water contact

(7) Agree to provide 3 consecutive daily urine samples every month for 10 months

(8) Agree to consult the study physician prior to taking any medication

C. Exclusion Criteria

(1) History of allergies to niclosamide or related compounds

(2) History of drug allergies, skin rash, seizures or chronic medical problems

(3) Presence of skin abnormalities or medical disorders deemed significant by the examining physician

(4) Another person residing in the same dwelling and participating in the study (i.e. only one person per household (residing under the same roof) may be enrolled in the study

Healthy male farmers aged 18 to 40 years who had recently been successfully treated for schistosomiasis and who fulfilled the trial inclusion criteria were invited to participate in the treatment trial. This treatment trial was endorsed by the Egyptian Ministry of Health and the local health district authorities and community acceptance was high due to the local awareness that schistosomiasis is a serious health problem in their villages.

Study Medication:

The drug used in this study was a 1% solution of niclosamide formulated in an ethyl alcohol-based lotion. The lotion, had the consistency of insect repellant or sunscreen lotion and was faintly yellow in color. The placebo lotion is the same formulation without the 1% niclosamide, but with a yellow dye compound to provide the same color to the lotion. Both lotions were identical in appearance and consistency. Study medication was manufactured by Miles Pharmaceuticals, Inc. which provided the lotion for this study under Cooperative Research and Development Agreement number DAMD17-86-0289 (U.S. Army Medical Research and Development Command). The lotion was packaged in 30 ml polyethylene bottles with screw-on caps.

Assignment of Study Medications:

The study used a double blinding procedure to assign drug to participants. The study medication and placebo were delivered to the Walter Reed Army Institute of Research, Division of Experimental Therapeutics (WRAIR-ET) by Miles Pharmaceuticals, Inc. Upon arrival at WRAIR-ET, the bottles were packaged in containers which identified them as either active drug, or placebo. At WRAIR-ET, the bottles were individually labeled with one of ten (10) letters (A,B,C,D,F,H,J,L,U,X), and a label identifying the contents as an Investigational New Drug, was affixed. These

were the only identification markings shown on the bottles as they were delivered to the study site. The medication was then delivered by air cargo service to Cairo, Egypt where it was stored in the pharmacy at United States Naval Medical Research Unit No.3 (NAMRU-3) at 25 to 28°C and issued to the field at periodic two weeks intervals.

Participants were assigned identification numbers, beginning at 001 and increasing sequentially to 600. The blinded, random assignment to study medication was provided by WRAIR, Division of Experimental Therapeutic (Parasitology) with the aid of a computerized statistical model. The blinding was blocked in groups of 20, i.e. within each group of twenty numbers each of the 10 letters would repeat exactly twice. The study medication was transported to the field sites, inventoried and stored in locked storage rooms at the village clinics, and was issued to the participants bi-weekly. Each participant received a box of eight bottles of study medication every two weeks. All drug bottles, used, unused, or partially used were returned to the study monitor bi-weekly for inventory and transport to NAMRU-3 for destruction by incineration.

The code identifying active and placebo niclosamide lotion was held only by the Commanding Officer, NAMRU-3 (medical monitor) and the product manager (sponsor's representative) at the U.S. Army Medical Material Development Activity, Ft. Detrick,

Maryland. No medical emergencies occurred during the study which required the composition of a subject's lotion to be disclosed.

Dosage Range:

The dosage of niclosamide varied slightly depending on the size (body surface area) of the individual subject. A single application consisted of enough lotion to cover the upper and lower limbs, neck and torso. The dosage ranged from one to two bottles per application. A subject properly applying niclosamide lotion, therefore, received a topical dose of 30 to 60 mg of niclosamide per application.

Dosage Schedule:

Lotion was self-applied under observation twice a week on Saturday and Tuesday, Sunday and Wednesday, or Monday and Thursday. Lotion was applied in the morning before the farmers went to work in the fields. Field monitors went to the study participants' homes two times per week on the designated days and observed the lotion application and collected water contact data.

Application of Study Medication:

The study participants self-applied the lotion by removing the cap from the bottle

and squeezing several milliliters from it into their hands and rubbing the lotion in a systematic pattern over their upper limbs from the shoulder down to the hands and fingers. They also applied it to their neck, chest, abdomen and back. Then, they applied the lotion to their lower limbs from the upper thigh down to the feet including the interdigital spaces of the toes and the soles. The study participants were helped by their wives, brothers, or study monitors in applying the lotion to their backs.

Concomitant Medications:

Medications which were considered necessary for the patient's welfare were given at the discretion of the principal investigator or the associate investigator. Any administration of such drugs was reported in the appropriate section of the medical form.

Duration of the Study:

The application of study medication began on April 11, 1992 in the four villages. Lotion application continued for 26 weeks terminating on October 8, 1992. The first 4 months (16 weeks) were the initial washout period. Data considered for statistical analysis on the efficacy of the lotion consisted of that collected from the end of the

washout period point until three months (12 weeks) following the end of application of the study medication. Collection and analysis of urine specimens, continued for four months (16 weeks) after application of the study medication had been discontinued. The last urine collections were on January 30, 31 and February 1, 1993 .

Study Procedures:

Approximately 4 to 5 months prior to the start of the study during November-December 1991, approximately 5000 male farmers were given a labelled 50 ml plastic centrifuge tube for urine and were asked to provide a urine specimen by the Fayoum Governate, Ministry of Health survey team. The specimens were processed for examination within 4-6 hours of collection. Urine samples were examined by the sedimentation concentration technique.[17] Praziquantel treatment was carried out during December 1991, based on the results of the urine and stool samples. Each subject with a urine positive for Schistosoma haematobium eggs received a single oral dose of 40 mg/kg of praziquantel under the supervision of a local Ministry of Health physician. Twelve weeks after treatment, which was one month prior to the start of application of the study medication, the Fayoum Governate, Ministry of Health survey team collected three urine samples on three consecutive days from all the treated subjects to identify eligible candidates for the study. Individuals found negative for S. haematobium during

this re-examination were considered as potential subjects for the trial and were referred to NAMRU-3 investigators. A careful medical history and physical examination were performed on each of the potential subjects with particular attention to the presence of rash or other skin abnormalities. From this pool of potential subjects, 600 volunteers were provided an oral single dose of 40 mg/kg body weight of praziquantel under the supervision of the NAMRU-3 principal investigators or the study physicians and entered into the study after providing written informed consent. The application of the study lotion began in April 11, 1992 and continued for 26 weeks.

Clinical Evaluations:

A. General

A study physician performed a medical history and physical examination on each participant. The medical history and physical data were recorded on Standard Form 600 (Appendix 1a) and filed along with the informed consent form.

B. Dermatologic Reactions

The subject was informed at the beginning of the study and at every re-evaluation

that the field monitor would ask him if he developed a skin rash during the study. The field monitor would notify the field coordinator who would evaluate the rash, noting its location, character, extent, other salient features, as well as the presence of accompanying symptoms such as nausea, dizziness or wheezing. The findings would be recorded by the field coordinator on the Dermal/Systemic Reaction Record (Appendix 2). The field coordinator would notify the study physician of his findings by telephone or directly the same day. The physician would evaluate all adverse reactions (local and systemic) utilizing the FDA from 1639, Adverse Reaction Report, (Appendix 3). If the rash was less than 20 cm in diameter and limited to one or two locations without serious accompanying symptoms, the subject would be re-examined daily by the field monitor and would continue to apply the test lotion and work in the field. Daily observation would occur until the rash had significantly diminished. If the rash area was over 20 cm in diameter, located in more than two sites, or was accompanied by serious symptoms such as severe pain, itching, swelling or weeping, the study physician would be immediately contacted and would evaluate the subject that day. The subject would be instructed not to apply the test lotion or engage in water-related work until satisfactory improvement was noted by the physician. The subject would be examined daily by the physician and if satisfactory improvement was not noted within 5 days the subject would be evaluated by the study's consulting dermatologist in

Cairo for appropriate investigations and therapy or the subject might select a physician of his choice for medical care. The medical care would continue until satisfactory improvement occurred and during that period the subject would not apply the test lotion or engage in water related agriculture activity until determined cured by the dermatology consultant. The subject would be compensated at the existing daily rate for loss of work due to required water avoidance procedures and related medical costs including transportation to the medical facility by the study group. If the subject was unable to safely re-apply the test lotion on the recommendation of the dermatology consultant or at the subject's choice, the subject would permanently discontinue application of the study lotion and resume normal work activities when determined medically advisable by the consulting dermatologist.

Field Evaluation:

Each participant was issued a box containing eight 30 ml bottles of the study lotion bi-weekly. Study subjects self-applied the lotion twice weekly on designated days (Saturday and Tuesday, Sunday and Wednesday, or Monday and Thursday) to their upper and lower limbs, neck and torso. Lotion application was monitored on days that it was applied. The lotion was applied in the morning before the study subjects left for work in the fields. Field monitors visited the study participants' houses early in the

morning two times per week on the designated days and observed the lotion application. At the same time, the field monitor collected data since the previous visit on water contact, unprotected exposure (body areas other than the upper and lower limbs, neck and torso) to canal or irrigation water and any adverse reactions to the lotion . The monitor recorded the data on each subject's record log. Each monitor was responsible for observing and documenting the activities of 10-15 study participants (3-5 participants each day). The study subjects also were visited once a week by a field coordinator who supervised the field monitor, observed lotion application and collected data for quality control. In addition, the principal investigators visited all participants at least once a month throughout the study duration to assess lotion application, water contact and local or systemic reactions. The data collected by the field monitor, the field coordinator, the senior supervisor and the principal investigators were routinely compared and discrepancies were investigated to assure protocol compliance.

The principal investigators monitored 600 study participants, supervised 49 field monitors, 16 local supervision teams (32 field coordinators) and 4 field supervisors (study physicians) (Table 1). The field monitor and coordinator were responsible for reporting to the principal investigators when compliance was not 100%. A missed application was defined as that in which the study drug was not applied as scheduled and

water contact occurred prior to the next application. Full compliance was expected from all study participants. When full compliance was not observed, the participant was counseled and the activities were appropriately recorded.

Laboratory Evaluations:

A. Collection of Specimens

Urine specimens were collected monthly after the start of lotion application and continued for 4 months after cessation of lotion application (Appendix 4). A single collection consisted of three consecutive daily specimens. All participants were given a labeled 50ml plastic centrifuge tube for urine and were asked to provide their second voided urine sample of the following morning and return it to the laboratory. The containers were labeled with the participant's name, study number, number of collection and the date of collection. Participants were informed of the critical importance of collecting the Second specimen of the morning. The individual was instructed to jump up and down a few times or engage in some other brief physical activity prior to providing the specimen. This activity helps to dislodge eggs from the walls of the bladder and increases the likelihood that if eggs are present, would be passed in the urine.

Within two hours after the specimen was collected, it was preserved by adding

0.1 gm of sodium azide to the specimen. Specimens were then sent to the NAMRU-3 laboratory for analysis.

B. Laboratory Facility and Technique

The principal laboratory for this study was the parasitology laboratory at NAMRU-3 (Cairo). Specimens were preserved and transported to Cairo within three days of collection. The laboratory was under the direct supervision of two of the associate investigators of this study. Specimens were analyzed using the Nuclepore filters to detect the presence of S. haematobium eggs [18] (Appendix 5).

C. Laboratory Validation

The performance of the parasitology laboratory (NAMRU-3) was validated by inter-laboratory and intra-laboratory quality control programs. The inter-laboratory quality control program was evaluated by a series of (open and blind) quality control specimens that were provided by the parasitology laboratory at the Walter Reed Army Institute of Research. These were urine specimens that had been identified by WRAIR as either positive or negative for S. haematobium eggs. The initial set of specimens, which was provided prior to the start of the study, consisted of 88 specimens. They were "open", i.e. the technicians were aware that they were analyzing Q.C. specimens. These specimens were analyzed using the same procedure as that used for the specimens of the study participants. Monthly thereafter, WRAIR sent approximately

ten specimens for analysis. These were analyzed "blindly", i.e. the technicians were not aware that they were analyzing Q.C. specimens. It was the responsibility of the Q.C. co-ordinator to "blind" these specimens to the technicians. These specimens were analyzed along with the study participant's specimens.

Specimens were sent from WRAIR to Cairo by express mail. The results were reported by telephone facsimile transmission to WRAIR within 3 days of examination, followed by written mailed reports. The laboratory was required to identify 90% of the samples correctly on each set of specimens. There were two incidence in which the required 90% accuracy was not achieved and the NAMRU-3 laboratory took corrective measures under the guidance of sponsor (USAMMDA product manager) and the principal investigator (NAMRU-3).

For the intra-laboratory quality control program; (a) 10% of the mounted filtrates from each of the ten urine collections were examined twice, (b) urine specimens verified as positive or negative for S. haematobium eggs were examined blindly among the study participants specimens. The technicians were required to identify 90% of the samples correctly on each set of specimens. The NAMRU-3 technicians did identify more than 90% of the intra-laboratory Q.C. specimens correctly. Details of the laboratory validation (methodology and results) are shown in appendix 6.

Statistical Evaluation:

All data entry and evaluation were completed before breaking the medication code. The Epi Info microcomputer programs produced at the Centers for Disease Control and the World Health Organization were used to create questionnaires and to enter data. To assure the accuracy of data entry, a double-entry system was utilized with two different operators entering data into two separate files. The files were then compared by a special program provided by the Epi Info and any differences were identified so that the non-duplicate entries could be reviewed and reconciled in the two files. Data entry was performed in the field continuously throughout the study. Statistical evaluations included contingency table and chi-square tests for detection of differences in re-infection rates between the treatment groups. *Student's t-test* was used to test for differences of means among study groups. All the statistics performed were 2-tail analyses. The odds ratios (OR) were used to estimate the protective effect and 95% confidence intervals were computed. Logistic regression analysis of data was performed using SPSS/PC V4.1 to adjust for possible confounding variables.

For the purposes of statistical analysis, a schistosomiasis-infected subject who was detected during the washout period in the first four months of lotion application was not included in the statistical analysis to exclude the possibility of pre-infection or incomplete eradication of infection by praziquantel treatment. A subject positive for

S.haematobium in any urine collection 5 months after the start of lotion application until 4 months following cessation of lotion application (in months 5-10) was considered a re-infection (medication failure). A subject was required to be negative in each urine collection during the months 5-10 to be considered not re-infected.

Criteria for the success of the trial included:

1) A statistically significant difference between the frequency of schistosomiasis infection among subject using the placebo-control lotion vs those using 1% niclosamide lotion.

2) No statistically significant difference in local and systemic side effects between subjects using the placebo control lotion vs those using 1% niclosamide lotion.

Monitoring of Study:

The sponsor's representative (USAMMDA product manager) inspected all study patients' medical records and corresponding portions of case report forms twice during the study; once in October 1991, and a second time in July 1992. These inspections were for the purpose of verifying the completeness and exactness of the data being

entered on the report from, to verify proper completion of informed consent forms and medical records, to ensure that all procedures were being conducted as specified by the study protocol.

Protection of Human Subjects:

Study volunteers were selected with the consent and advice of the Ministry of Health, Arab Republic of Egypt. The purpose of the study, including the risks and benefits involved with participation, the right to withdraw at any time, and the circumstances under which the subject may be removed from the study by the principal investigator were explained to the subjects in their native Arabic language by a study physician.

Special care was taken to insure that each volunteer understood that he had the right to withdraw from the study at any time, that he need not provide a reason for withdrawal, that withdrawal would be without prejudice, and that he would be eligible for medical care for schistosomiasis throughout the duration of the study whether or not he had completed the study.

Ethical Aspects:

A. Institutional Review Board

The protocol was reviewed and approved by the human use committees of the U.S. Naval Medical Research Unit #3 (Cairo) and the U.S. Army Surgeon General (Human Subjects Research Review Board).

B. Informed Consent

The voluntary signature of each subject was obtained on the informed consent form which was in Arabic (Appendix 6b). The Arabic consent form was an exact translation of the attached English consent form (Appendix 6a). All signatures were in black ink using a ball point pen. Felt tipped or fountain pens were not allowed, as the ink tends to fade and/or run. Black ink only was used to facilitate photocopying.

Prior to signing of the informed consent form, the general purpose of the study was explained to the subject. Each participant had the informed consent form read to him, and had the opportunity to ask questions before signing. The consent form contained the name and address of the participant, the date the informed consent was executed, the participant's signature, and the name and signature of the witness. The field monitors, field coordinators, and the study physicians served as witnesses.

All the forms were stored in the corresponding village clinics in locked rooms.

At the end of the study, all forms were archived with the data at NAMRU-3 in Cairo in the Clinical Investigation Division records file.

Disposition of Study Materials:

A. Drug Inventory

The central drug inventory was maintained in the central pharmacy at NAMRU-3 (Cairo). From that point, a portion of the inventory was moved to the field on a bi-weekly basis. The drug was dispensed by the NAMRU-3 pharmacist who maintained inventory records. The medical supplies were transported to the village clinics, where the drug was stored in a locked room in the clinic. From the clinical sites, the field monitors dispensed the drug to the participants giving each a two-week supply (8 bottles) at a time. The dispensing of the drug to the participant was done utilizing a master log showing the participant's study number and assigned medication code.

B. Unused Drug

All unused drug and all empty bottles were returned by the participants to the field monitors. The returned drug was recorded and all unused medications were transported to NAMRU-3 (Cairo). The returned drug was confirmed against the master log by the principal investigator and then destroyed by incineration.

C. Case Report Forms

The case report forms (Appendix 7) for each subject were transported from the field bi-weekly and maintained in the Epidemiology Division NAMRU-3 in a secured cabinet. All entries were made in indelible black ink. All corrections that were made to the forms were made with a simple line through the error, dated and initialed with the correction written to the side. The case report forms were filed bi-weekly, with the forms maintained in a chronological order with a tracking system. The investigators reviewed the forms bi-weekly for compliance with the above requirements.

Results

Of the 600 farmers participating in the study (Figure 1, Table 2), 250 required exclusion from the statistical analysis for the following reasons: one hundred and sixty one (64.4%) were eliminated due to the presence of S. haematobium eggs in one or more urine specimen collection conducted in the first 4 months of the study; twenty six (10.4%) were eliminated because of non compliance with the study procedures; twenty three (9.2%) refused to continue for no specific reason; twenty nine (11.6%) temporarily left the study area and 11 (4.4%) were disqualified for other reasons (Table 3). A total of 350 subjects met the inclusion criteria and were included in the statistical analysis (Table 4). Ninety three (26.6%) subjects were from Musharak Bahary, 90

(25.7%) from Musharak Qebly, 59 (16.9%) from Kahk and 108 (30.9%) from Batn Ehrit (Table 5). One hundred sixty nine (48.3%) subjects were using the 1% niclosamide lotion and 181 (51.7%) were applying the placebo lotion (Table 6). The mean age of the subjects was 27.5 years, which was nearly identical for the two groups. There was no significant difference in age between the two study groups among the four villages (Table 7). The subjects' compliance with lotion application was exceptionally good,with 332 (92%) reporting lotion application bi-weekly for 26 weeks with no more than one missed application. In the niclosamide group 158 (93.5%) subjects reported lotion application for the entire study period with no more than one missed application compared to 168 (90.6%) in the placebo group (Table 8). There was no difference in lotion application compliance among the two groups. Lotion application was observed by study monitors in 90% or more of the occasions in 155 (91.7%) subjects in the niclosamide group versus 157 (86.7%) of the subjects in the placebo group (Table 9). The difference in observation between the two groups was not statistically significant. The mean total canal or irrigation water contact during the entire study period was 101.9 $\pm$ 47.7 hours in subjects recieving niclosamide and 109.0$\pm$ 52.8 hours in subjects receiving placebo lotion (Table 10). No significant difference in mean total infested water contact was noted among the two groups. An analysis of variance and Scheffe's multiple range test, revealed statistical significance

in mean total infested water contact only among Musharak Bahary and Musharak Qebly. Subjects receiving niclosamide and placebo lotion were comparable in reported water contact by skin other than the lotion application areas. One hundred sixty (94.7%) subjects in the niclosamide group versus 175 (96.7%) in the placebo group reported no water contact of non-lotion application skin surface areas (Table 11). No statistical difference was noted in reported unprotected water contact between the two study groups. The re-infection rate of S. haematobium during the study based on the presence of live and dead ova in urine up to 12 weeks after cessation of lotion application was 30.8% in the niclosamide group and 28.2% in placebo the group (Table 12). The re-infection rates up to 16 weeks were 37.3% and 32.0% in the niclosamide and placebo groups, respectively (Table 13). The re-infection rates based on the presence of live ova only up to 12 weeks was 10.7% in the niclosamide group and 11.6% in the placebo group (Table 14). The re-infection rate up to 16 weeks was 14.2% and 13.8% in the niclosamide and placebo groups respectively (Table 15). There were no statistically significant difference in re-infection rates between the two study groups.

One subject had an adverse reaction to the lotion. He was withdrawn from the study and treated successfully. This adverse reaction was reported to the sponsor as required. Because the subject was successfully treated, it was not necessary to break

the study code. It was noted at the conclusion of the study that the subject had applied placebo, i.e. his reaction was probably in allergic reaction to the (alcoholic) lotion vehicle.

Discussion

One percent niclosamide lotion was noted to be effective in the prevention of re-infection with S. mansoni in Egyptian farmers in the Nile Delta utilizing a daily self-application regimen for a 5-months exposure period. [12] The present study reveals no protective effect with the use of 1% niclosamide lotion utilizing a twice per week self-application regimen. The lotion application period for both studies was almost identical, although the average total infested water exposure was greater in the S. mansoni trial (180 hours) than in the present study (106 hours). The lotion application in this study involved greater body contact surface area which included limbs, torso, and neck as compared to only limb in the S. mansoni study. The twice weekly self application regimen to the arms and the trunk was well accepted by the farmers and a high level of compliance was observed. No skin or systemic reaction occurred which require discontinuation of lotion application.

The reasons for a lack of protection by niclosamide lotion in this study are most likely either a lack of adequate schistosome anti-penetrant activity against S.

haematobium cercariae or inadequate residual anti-penetrant activity of niclosamide lotion when used in an intermittent twice per week application schedule. Previous studies in monkeys showed that niclosamide was effective in preveting re-infection with both S. mansoni and S. haematobium [7,9]. If the latter explanation is the reason for the failure of protection in this study, acceptable protection might be obtained utilizing a more intensive application regimen such as a daily or alternate-day schedule or application immediately prior to infested water contact. Moreover, protection might be obtained with the use of niclosamide lotion in short exposure-time situations such as brief encounters with infested water during activities such as water crossing or boating.

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TABLE 1

Individuals participating in the field operations

600	Study Participating
49	Field Monitors
32	Field Coordinators
4	Field Supervisors (Study Physicians)

TABLE 2

The Status of the 600 subjects participating in the study

SUBJECT ID	VILLAGE	INCLUDED IN THE STUDY	REASON FOR EXCLUSION	LAST STOOL SPECIMEN SUBMITTED	FINAL RESULT
1	1	N	Pos in Col. 2 & 4	10	.
2	1	Y	.	.	Y
3	1	N	No Specimen for Col. 3	10	.
4	1	Y	.	.	N
5	1	Y	.	.	N
6	1	N	Pos in Col. 3	.	.
7	1	N	Travel outside study area	3	.
8	1	N	Pos in Col. 2	10	.
9	1	Y	.	.	N X
10	1	Y	.	.	N
11	1	N	Pos in Col. 2 & 3 & 4	10	.
12	1	Y	.	.	N
13	1	N	Pos in Col. 2	10	.
14	1	N	Disqualified by Age	4	.
15	1	Y	.	.	N
16	1	Y	.	.	Y
17	1	Y	.	.	Y
18	1	Y	.	.	N
19	1	Y	.	.	N
20	1	Y	.	.	N
21	1	Y	.	.	N
22	1	N	Pos in Col. 2 & 4	10	.
23	1	N	Pos in Col. 3	10	.
24	1	N	Pos in Col. 2 & 3 & 4	10	.
25	1	Y	.	.	N
26	1	Y	.	.	Y
27	1	Y	.	.	N
28	1	Y	.	.	N
29	1	N	Pos in Col. 3 & 4	10	.
30	1	N	No Specimen for Col. 3	10	.
31	1	N	Pos in Col. 3	4	.
32	1	N	Pos in Col. 4	10	.
33	1	N	Pos in Col. 3	10	.
34	1	N	Pos in Col. 2 & 3	10	.
35	1	Y	.	.	Y
36	1	N	Pos in Col. 2 & 4	10	.
37	1	N	Pos in Col. 2	10	.
38	1	Y	.	.	N
39	1	Y	.	.	N
40	1	Y	.	.	N
41	1	N	Pos in Col. 3	10	.
42	1	Y	.	.	N
43	1	Y	.	.	Y

Village "1= Musharak Bahary 2= Musharak Qebly 3= Kahk 4= Batn Ehrit"

SUBJECT ID	VILLAGE	INCLUDED IN THE STUDY	REASON FOR EXCLUSION	LAST STOOL SPECIMEN SUBMITTED	FINAL RESULT
44	1	N	Pos in Col. 4	10	.
45	1	Y	.	.	N
46	1	Y	.	.	N
47	1	Y	.	.	Y
48	1	N	Refused to continue	0	.
49	1	Y	.	.	Y
50	1	Y	.	.	Y
51	1	Y	.	.	N
52	1	Y	.	.	Y
53	1	Y	.	.	Y
54	1	Y	.	.	N
55	1	N	Pos in Col. 2 & 4	10	.
56	1	Y	.	.	N
57	1	Y	.	.	N
58	1	Y	.	.	N
59	1	Y	.	.	N
60	1	Y	.	.	Y
61	1	N	Travel outside study area	4	.
62	1	Y	.	.	N
63	1	N	Pos in Col. 2	10	.
64	1	Y	.	.	Y
65	1	Y	.	.	N
66	1	N	Travel outside study area	3	.
67	1	Y	.	.	Y
68	1	Y	.	.	Y
69	1	Y	.	.	N
70	1	Y	.	.	N
71	1	Y	.	.	Y
72	1	Y	.	.	Y
73	1	N	Pos in Col. 2	10	.
74	1	Y	.	.	Y
75	1	Y	.	.	N
76	1	Y	.	.	N
77	1	Y	.	.	N
78	1	Y	.	.	N
79	1	N	Travel outside study area	3	.
80	1	Y	.	.	N
81	1	N	Refused to continue	3	.
82	1	N	Travel outside study area	2	.
83	1	Y	.	.	Y
84	1	N	Pos in Col. 4	10	.
85	1	Y	.	.	N
86	1	N	Pos in Col. 4	10	.
87	1	N	Pos in Col. 2 & 4	10	.
88	1	Y	.	.	N
89	1	Y	.	.	N
90	1	Y	.	.	N
91	1	N	Pos in Col. 3	10	.

SUBJECT ID	VILLAGE	INCLUDED IN THE STUDY	REASON FOR EXCLUSION	LAST STOOL SPECIMEN SUBMITTED	FINAL RESULT
92	1	Y	.	.	N
93	1	N	Travel outside study area	0	.
94	1	N	Pos in Col. 4	10	.
95	1	N	Non Compliance	10	.
96	1	N	Refused to continue	2	.
97	1	Y	.	.	Y
98	1	N	Pos in Col. 3	10	.
99	1	Y	.	.	N
100	1	Y	.	.	N
101	1	Y	.	.	N
102	1	Y	.	.	Y
103	1	Y	.	.	N
104	1	Y	.	.	Y
105	1	N	Pos in Col. 2	10	.
106	1	Y	.	.	Y
107	1	Y	.	.	Y
108	1	N	Non Compliance	10	.
109	1	Y	.	.	Y
110	1	N	Pos in Col. 2	10	.
111	1	Y	.	.	Y
112	1	Y	.	.	N
113	1	N	Pos in Col. 3	10	.
114	1	Y	.	.	Y
115	1	Y	.	.	N
116	1	Y	.	.	N
117	1	N	Used the wrong lotion	4	.
118	1	N	Used the wrong lotion	4	.
119	1	Y	.	.	N
120	1	Y	.	.	N
121	1	N	Disqualified by Age	4	.
122	1	Y	.	.	N
123	1	Y	.	.	N
124	1	N	Pos in Col. 2	10	.
125	1	Y	.	.	Y
126	1	Y	.	.	N
127	1	N	Disqualified by Age	4	.
128	1	N	Pos in Col. 3	10	.
129	1	N	No Specimen for Col. 4	10	.
130	1	Y	.	.	Y
131	1	N	Pos in Col. 3	10	.
132	1	Y	.	.	Y
133	1	N	Pos in Col. 2	10	.
134	1	Y	.	.	N
135	1	N	Pos in Col. 3	10	.
136	1	N	Disqualified by Age	4	.
137	1	N	Travel outside study area	0	.
138	1	Y	.	.	N
139	1	N	Pos in Col. 4	10	.

SUBJECT ID	VILLAGE	INCLUDED IN THE STUDY	REASON FOR EXCLUSION	LAST STOOL SPECIMEN SUBMITTED	FINAL RESULT
140	1	N	Travel outside study area	0	.
141	1	N	Pos in Col. 3	10	.
142	1	Y	.	.	Y
143	1	N	Pos in Col. 3	10	.
144	1	Y	.	.	Y
145	1	Y	.	.	Y
146	1	Y	.	.	Y
147	1	Y	.	.	N
148	1	Y	.	.	N
149	1	N	Travel outside study area	3	.
150	1	Y	.	.	Y
151	1	Y	.	.	Y
152	1	N	Pos in Col. 2	10	.
153	1	N	Pos in Col. 2	10	.
154	1	N	Pos in Col. 2 & 3	10	.
155	1	N	Pos in Col. 2	10	.
156	1	N	Pos in Col. 3	10	.
157	1	Y	.	.	N
158	1	Y	.	.	N
159	1	N	Pos in Col. 2 & 3	10	.
160	1	N	Pos in Col. 3 & 4	10	.
161	2	Y	.	.	N
162	2	Y	.	.	N
163	2	N	Pos in Col. 2	10	.
164	2	N	Pos in Col. 4	10	.
165	2	N	Pos in Col. 2	10	.
166	2	Y	.	.	Y
167	2	N	Pos in Col. 3	10	.
168	2	Y	.	.	N
169	2	Y	.	.	Y
170	2	Y	.	.	N
171	2	N	Pos in Col. 4	10	.
172	2	Y	.	.	N
173	2	N	Pos in Col. 3	10	.
174	2	N	Travel outside study area	1	.
175	2	Y	.	.	Y
176	2	Y	.	.	Y
177	2	Y	.	.	Y
178	2	Y	.	.	Y
179	2	Y	.	.	N
180	2	N	Pos in Col. 2 & 4	10	.
181	2	Y	.	.	Y
182	2	N	Pos in Col. 2 & 4	10	.
183	2	N	Travel outside study area	0	.
184	2	Y	.	.	Y
185	2	N	Pos in Col. 2 & 3	10	.
186	2	N	Pos in Col. 3 & 4	10	.
187	2	Y	.	.	N

SUBJECT ID	VILLAGE	INCLUDED IN THE STUDY	REASON FOR EXCLUSION	LAST STOOL SPECIMEN SUBMITTED	FINAL RESULT
188	2	Y	.	.	Y
189	2	Y	.	.	N
190	2	N	Pos in Col. 3 & 4	10	.
191	2	Y	.	.	N
192	2	N	Travel outside study area	2	.
193	2	N	Pos in Col. 2	10	.
194	2	Y	.	.	Y
195	2	N	Non Compliance	10	.
196	2	N	Pos in Col. 2 & 3	10	.
197	2	Y	.	.	Y
198	2	Y	.	.	Y
199	2	N	Pos in Col. 3 & 4	10	.
200	2	Y	.	.	Y
201	2	Y	.	.	Y
202	2	N	Pos in Col. 2	10	.
203	2	Y	.	.	N
204	2	Y	.	.	N
205	2	Y	.	.	N
206	2	Y	.	.	N
207	2	Y	.	.	N
208	2	Y	.	.	N
209	2	Y	.	.	N
210	2	Y	.	.	N
211	2	N	Pos in Col. 4	10	.
212	2	N	Pos in Col. 3 & 4	10	.
213	2	Y	.	.	N
214	2	N	Pos in Col. 4	10	.
215	2	N	Pos in Col. 2 & 3 & 4	10	.
216	2	N	Pos in Col. 2	10	.
217	2	N	Pos in Col. 4	10	.
218	2	Y	.	.	N
219	2	Y	.	.	N
220	2	N	Pos in Col. 3 & 4	6	.
221	2	Y	.	.	N
222	2	Y	.	.	N
223	2	Y	.	.	N
224	2	N	Pos in Col. 4	10	.
225	2	Y	.	.	Y
226	2	N	Pos in Col. 2	10	.
227	2	Y	.	.	N
228	2	N	Pos in Col. 2 & 4	10	.
229	2	Y	.	.	Y
230	2	Y	.	.	Y
231	2	N	No Specimen for Col. 3	10	.
232	2	Y	.	.	N
233	2	Y	.	.	N
234	2	N	Non Compliance	10	.
235	2	Y	.	.	N

SUBJECT ID	VILLAGE	INCLUDED IN THE STUDY	REASON FOR EXCLUSION	LAST STOOL SPECIMEN SUBMITTED	FINAL RESULT
236	2	Y	.	.	N
237	2	N	Pos in Col. 4	10	.
238	2	Y	.	.	N
239	2	Y	.	.	N
240	2	Y	.	.	Y
241	2	Y	.	.	N
242	2	N	Pos in Col. 2	10	.
243	2	Y	.	.	Y
244	2	N	Pos in Col. 2	10	.
245	2	Y	.	.	N
246	2	Y	.	.	Y
247	2	Y	.	.	N
248	2	Y	.	.	Y
249	2	N	Pos in Col. 3	10	.
250	2	N	Pos in Col. 2 & 3 & 4	10	.
251	2	Y	.	.	N
252	2	N	Zero Water Contact	10	.
253	2	Y	.	.	N
254	2	Y	.	.	Y
255	2	N	Zero Water Contact	10	.
256	2	Y	.	.	N
257	2	Y	.	.	N
258	2	Y	.	.	N
259	2	N	Pos in Col. 4	10	.
260	2	N	Pos in Col. 2	10	.
261	2	N	Travel outside study area	1	.
262	2	N	Pos in Col. 3	10	.
263	2	N	Travel outside study area	1	.
264	2	N	Travel outside study area	3	.
265	2	Y	.	.	N
266	2	Y	.	.	N
267	2	Y	.	.	N
268	2	Y	.	.	N
269	2	Y	.	.	N
270	2	N	Travel outside study area	2	.
271	2	Y	.	.	N
272	2	N	No Specimen for Col. 6 & 7	.	.
273	2	Y	.	.	N
274	2	Y	.	.	Y
275	2	Y	.	.	N
276	2	N	Travel outside study area	1	.
277	2	Y	.	.	Y
278	2	N	Pos in Col. 4	10	.
279	2	Y	.	.	Y
280	2	Y	.	.	N
281	2	Y	.	.	N
282	2	N	Pos in Col. 3	10	.
283	2	Y	.	.	Y

SUBJECT ID	VILLAGE	INCLUDED IN THE STUDY	REASON FOR EXCLUSION	LAST STOOL SPECIMEN SUBMITTED	FINAL RESULT
284	2	Y	.	.	Y
285	2	N	Non Compliance	10	.
286	2	Y	.	.	N
287	2	N	Pos in Col. 2 & 4	10	.
288	2	Y	.	.	N
289	2	N	Pos in Col. 3	10	.
290	2	Y	.	.	N
291	2	Y	.	.	Y
292	2	Y	.	.	Y
293	2	Y	.	.	N
294	2	N	Pos in Col. 3	10	.
295	2	Y	.	.	N
296	3	Y	.	.	N
297	3	N	Non Compliance	10	.
298	3	Y	.	.	N
299	3	Y	.	.	N
300	3	N	Pos in Col. 2 & 4	10	.
301	3	N	Non Compliance	10	.
302	3	N	Non Compliance	10	.
303	3	Y	.	.	N
304	3	N	Pos in Col. 4	10	.
305	3	Y	.	.	N
306	3	N	Pos in Col. 2	10	.
307	3	Y	.	.	N
308	3	N	Pos in Col. 4	10	.
309	3	Y	.	.	N
310	3	Y	.	.	N
311	3	N	Pos in Col. 4	10	.
312	3	N	Refused to continue	3	.
313	3	N	Refused to continue	2	.
314	3	Y	.	.	N
315	3	Y	.	.	N
316	3	N	Refused to continue	2	.
317	3	Y	.	.	N
318	3	Y	.	.	N
319	3	N	No Specimen for Col. 10	9	.
320	3	N	Pos in Col. 3	.	.
321	3	Y	.	.	Y
322	3	N	Refused to continue	0	.
323	3	Y	.	.	Y
324	3	N	Refused to continue	2	.
325	3	Y	.	.	N
326	3	N	Refused to continue	1	.
327	3	N	Pos in Col. 4	10	.
328	3	Y	.	.	N
329	3	N	Non Compliance	10	.
330	3	N	Non Compliance	10	.
331	3	N	Non Compliance	10	.

SUBJECT ID	VILLAGE	INCLUDED IN THE STUDY	REASON FOR EXCLUSION	LAST STOOL SPECIMEN SUBMITTED	FINAL RESULT
332	3	N	Pos in Col. 2	10	.
333	3	Y	.	.	N
334	3	N	Refused to continue	2	.
335	3	Y	.	.	N
336	3	Y	.	.	Y
337	3	Y	.	.	N
338	3	N	Pos in Col. 2 & 4	10	.
339	3	N	Refused to continue	3	.
340	3	Y	.	.	N
341	3	N	Travel outside study area	3	.
342	3	N	Disqualified by Age	4	.
343	3	N	Pos in Col. 2 & 4	10	.
344	3	N	Pos in Col. 3 & 4	10	.
345	3	N	Pos in Col. 4	10	.
346	3	N	Pos in Col. 3	10	.
347	3	Y	.	.	Y
348	3	Y	.	.	Y
349	3	Y	.	.	N
350	3	Y	.	.	N
351	3	Y	.	.	Y
352	3	Y	.	.	N
353	3	Y	.	.	N
354	3	Y	.	.	N
355	3	Y	.	.	N
356	3	N	Pos in Col. 4	10	.
357	3	Y	.	.	N
358	3	Y	.	.	N
359	3	Y	.	.	N
360	3	N	Pos in Col. 4	10	.
361	3	N	Pos in Col. 2 & 4	10	.
362	3	N	Refused to continue	1	.
363	3	N	Pos in Col. 4	10	.
364	3	Y	.	.	N
365	3	Y	.	.	N
366	3	N	Refused to continue	0	.
367	3	Y	.	.	N
368	3	Y	.	.	Y
369	3	N	Refused to continue	3	.
370	3	N	Non Compliance	10	.
371	3	Y	.	.	Y
372	3	Y	.	.	N
373	3	Y	.	.	Y
374	3	N	Refused to continue	4	.
375	3	Y	.	.	Y
376	3	Y	.	.	Y
377	3	N	Pos in Col. 4	10	.
378	3	Y	.	.	N
379	3	Y	.	.	Y

SUBJECT ID	VILLAGE	INCLUDED IN THE STUDY	REASON FOR EXCLUSION	LAST STOOL SPECIMEN SUBMITTED	FINAL RESULT
380	3	Y	.	.	Y
381	3	Y	.	.	N
382	3	Y	.	.	Y
383	3	Y	.	.	N
384	3	N	Travel outside study area	7	.
385	3	Y	.	.	Y
386	3	Y	.	.	N
387	3	Y	.	.	Y
388	3	Y	.	.	N
389	3	N	Non Compliance	10	.
390	3	N	Pos in Col. 4	10	.
391	3	N	*VTCNE for Col. 10	10	.
392	3	N	*VTCNE for Col. 10	10	.
393	3	Y	.	.	Y
394	3	N	Travel outside study area	6	.
395	3	Y	.	.	N
396	3	Y	.	.	N
397	3	Y	.	.	N
398	3	Y	.	.	N
399	3	Y	.	.	N
400	3	Y	.	.	N
401	4	Y	.	.	N
402	4	Y	.	.	Y
403	4	N	Pos in Col. 4	10	.
404	4	N	Pos in Col. 3	10	.
405	4	Y	.	.	Y
406	4	N	Pos in Col. 4	10	.
407	4	N	Pos in Col. 2	10	.
408	4	N	Pos in Col. 4	10	.
409	4	N	Pos in Col. 4	10	.
410	4	Y	.	.	N
411	4	N	Pos in Col. 3	10	.
412	4	Y	.	.	N
413	4	N	Pos in Col. 4	10	.
414	4	Y	.	.	Y
415	4	Y	.	.	N
416	4	N	Non Compliance	10	.
417	4	N	Pos in Col. 2	10	.
418	4	Y	.	.	N
419	4	N	Refused to continue	0	.
420	4	N	Non Compliance	10	.
421	4	N	Refused to continue	0	.
422	4	Y	.	.	N
423	4	Y	.	.	Y
424	4	N	Pos in Col. 3	10	.

* VTCNE = Very Thick Can not be Eexamined

SUBJECT ID	VILLAGE	INCLUDED IN THE STUDY	REASON FOR EXCLUSION	LAST STOOL SPECIMEN SUBMITTED	FINAL RESULT
425	4	Y	.	.	Y
426	4	Y	.	.	N
427	4	Y	.	.	N
428	4	Y	.	.	N
429	4	Y	.	.	N
430	4	N	Pos in Col. 4	10	.
431	4	Y	.	.	N
432	4	Y	.	.	N
433	4	Y	.	.	N
434	4	N	Refused to continue	0	.
435	4	N	Pos in Col. 4	10	.
436	4	Y	.	.	N
437	4	N	Refused to continue	3	.
438	4	Y	.	.	N
439	4	Y	.	.	Y
440	4	Y	.	.	N
441	4	Y	.	.	Y
442	4	Y	.	.	N
443	4	Y	.	.	N
444	4	Y	.	.	Y
445	4	Y	.	.	N
446	4	N	Pos in Col. 2 & 4	10	.
447	4	Y	.	.	Y
448	4	Y	.	.	N
449	4	Y	.	.	N
450	4	Y	.	.	Y
451	4	Y	.	.	Y
452	4	Y	.	.	N
453	4	Y	.	.	N
454	4	N	Refused to continue	3	.
455	4	N	Travel outside study area	5	.
456	4	Y	.	.	Y
457	4	Y	.	.	Y
458	4	N	Travel outside study area	3	.
459	4	N	Pos in Col. 2 & 4	10	.
460	4	N	Pos in Col. 4	10	.
461	4	Y	.	.	N
462	4	Y	.	.	N
463	4	Y	.	.	N
464	4	Y	.	.	N
465	4	Y	.	.	N
466	4	Y	.	.	Y
467	4	Y	.	.	Y
468	4	Y	.	.	N
469	4	N	Pos in Col. 2	10	.
470	4	N	Pos in Col. 2	10	.
471	4	N	Pos in Col. 2	10	.
472	4	Y	.	.	Y

SUBJECT ID	VILLAGE	INCLUDED IN THE STUDY	REASON FOR EXCLUSION	LAST STOOL SPECIMEN SUBMITTED	FINAL RESULT
473	4	Y	.	.	N
474	4	N	Pos in Col. 2 & 3	10	.
475	4	N	Pos in Col. 3	10	.
476	4	Y	.	.	N
477	4	Y	.	.	N
478	4	Y	.	.	N
479	4	N	Pos in Col. 2	10	.
480	4	N	Pos in Col. 2	10	.
481	4	Y	.	.	Y
482	4	N	Non Compliance	10	.
483	4	N	Pos in Col. 3	10	.
484	4	Y	.	.	Y
485	4	Y	.	.	N
486	4	N	Pos in Col. 3	10	.
487	4	N	Pos in Col. 4	10	.
488	4	N	Pos in Col. 3	10	.
489	4	Y	.	.	Y
490	4	Y	.	.	N
491	4	Y	.	.	N
492	4	N	Pos in Col. 4	10	.
493	4	Y	.	.	N
494	4	N	Pos in Col. 2	10	.
495	4	N	Pos in Col. 4	10	.
496	4	N	Pos in Col. 2 & 3	10	.
497	4	N	Pos in Col. 4	10	.
498	4	Y	.	.	N
499	4	N	Pos in Col. 2	10	.
500	4	Y	.	.	Y
501	4	N	Pos in Col. 2	10	.
502	4	N	Pos in Col. 4	10	.
503	4	Y	.	.	Y
504	4	Y	.	.	Y
505	4	Y	.	.	N
506	4	Y	.	.	N
507	4	N	Pos in Col. 4	10	.
508	4	N	Pos in Col. 4	10	.
509	4	Y	.	.	Y
510	4	Y	.	.	Y
511	4	Y	.	.	Y
512	4	Y	.	.	N
513	4	N	Pos in Col. 4	10	.
514	4	Y	.	.	N
515	4	N	Pos in Col. 4	10	.
516	4	Y	.	.	Y
517	4	Y	.	.	N
518	4	N	Pos in Col. 4	10	.
519	4	Y	.	.	Y
520	4	Y	.	.	Y

SUBJECT ID	VILLAGE	INCLUDED IN THE STUDY	REASON FOR EXCLUSION	LAST STOOL SPECIMEN SUBMITTED	FINAL RESULT
521	4	N	No Specimen for Col. 4	10	.
522	4	Y	.	.	Y
523	4	Y	.	.	Y
524	4	N	Pos in Col. 3	10	.
525	4	Y	.	.	N
526	4	Y	.	.	N
527	4	N	Pos in Col. 2	10	.
528	4	Y	.	.	Y
529	4	Y	.	.	N
530	4	Y	.	.	N
531	4	Y	.	.	N
532	4	Y	.	.	N
533	4	N	Pos in Col. 3 & 4	10	.
534	4	N	Pos in Col. 3 & 4	10	.
535	4	N	Pos in Col. 2	10	.
536	4	Y	.	.	N
537	4	Y	.	.	N
538	4	Y	.	.	N
539	4	N	Pos in Col. 4	10	.
540	4	N	Pos in Col. 3	9	.
541	4	Y	.	.	N
542	4	N	Refused to continue	1	.
543	4	N	Non Compliance	10	.
544	4	N	Pos in Col. 3	10	.
545	4	Y	.	.	N
546	4	N	Travel outside study area	.	.
547	4	N	Travel outside study area	.	.
548	4	Y	.	.	N
549	4	N	Pos in Col. 2	10	.
550	4	Y	.	.	N
551	4	Y	.	.	N
552	4	Y	.	.	N
553	4	Y	.	.	Y
554	4	Y	.	.	Y
555	4	N	Travel outside study area	3	.
556	4	Y	.	.	N
557	4	N	Travel outside study area	4	.
558	4	N	Refused to continue	1	.
559	4	Y	.	.	N
560	4	Y	.	.	N
561	4	N	Pos in Col. 3 & 4	10	.
562	2	N	Travel outside study area	0	.
563	4	Y	.	.	Y
564	4	N	Pos in Col. 2 & 3	10	.
565	4	Y	.	.	N
566	4	N	Travel outside study area	2	.
567	4	Y	.	.	N
568	2	Y	.	.	N

SUBJECT ID	VILLAGE	INCLUDED IN THE STUDY	REASON FOR EXCLUSION	LAST STOOL SPECIMEN SUBMITTED	FINAL RESULT
569	4	N	Refused to continue	0	.
570	4	N	Pos in Col. 3	10	.
571	4	N	Pos in Col. 3	10	.
572	4	N	Pos in Col. 3	10	.
573	4	Y	.	.	Y
574	4	Y	.	.	N
575	4	N	Pos in Col. 4	10	.
576	4	Y	.	.	N
577	4	Y	.	.	N
578	4	Y	.	.	N
579	4	N	Pos in Col. 4	10	.
580	4	Y	.	.	Y
581	4	N	Pos in Col. 2 & 4	10	.
582	4	N	Pos in Col. 4	10	.
583	4	Y	.	.	N
584	4	N	No Specimen for Col. 2	10	.
585	4	Y	.	.	N
586	2	Y	.	.	Y
587	2	Y	.	.	N
588	4	Y	.	.	N
589	2	N	Travel outside study area	2	.
590	4	Y	.	.	N
591	2	N	Pos in Col. 2 & 3 & 4	10	.
592	4	Y	.	.	N
593	2	Y	.	.	N
594	2	Y	.	.	N
595	2	N	No Specimen for Col. 2 & 3	10	.
596	2	Y	.	.	Y
597	2	Y	.	.	Y
598	2	Y	.	.	N
599	2	N	Pos in Col. 2	10	.
600	2	N	Pos in Col. 2 & 3 & 4	10	.

TABLE 3
Reason for exclusion and discontinuation of subjects in the study villages

Reason for Exclusion	Musha. Bahary	Musha. Qebly	Batn Khak	Ehrit	Total
Disqualified by Age	4	0	1	0	5
No Specimen for Col. 10	0	0	1	0	1
No Specimen for Col. 2	0	0	0	1	1
No Specimen for Col. 2 & 3	0	1	0	0	1
No Specimen for Col. 3	2	1	0	0	3
No Specimen for Col. 4	1	0	0	1	2
No Specimen for Col. 6 & 7	0	1	0	0	1
Non Compliance	2	3	8	4	17
Pos in Col. 2	12	10	2	13	37
Pos in Col. 2 & 3	3	2	0	3	8
Pos in Col. 2 & 3 & 4	2	4	0	0	6
Pos in Col. 2 & 4	5	4	4	3	16
Pos in Col. 3	14	7	2	13	36
Pos in Col. 3 & 4	2	5	1	3	11
Pos in Col. 4	6	9	10	22	47
Refused to continue	3	0	12	8	23
Travel outside study area	9	10	3	7	29
Used the wrong lotion	2	0	0	0	2
*VTCNE for Col. 10	0	0	2	0	2
Zero Water Contact	0	2	0	0	2
Total	67	59	46	78	250

*Specimen for Col. 10 were very thick could not be examined.

TABLE 4

List of subjects included in the statistical analysis

SERIAL NO.	SUBJECT ID.	VILLAGE	AGE	TREAT CODE	FINAL RESULT	%LOTION APPLICA	%LOTION OBSERVA	TOTAL WATER EXPOS	UN-PROT EXPOSUR	SKIN COMP
1	2	1	19	1	Y	100	100	76	0	0
2	4	1	25	0	N	100	100	75	0	0
3	5	1	35	0	N	100	100	72	0	0
4	9	1	25	1	N	100	100	87	0	0
5	10	1	23	1	N	100	100	126	0	0
6	12	1	28	0	N	100	96	71	0	0
7	15	1	23	0	N	100	100	111	0	0
8	16	1	19	0	Y	100	100	72	0	0
9	17	1	39	1	Y	98	98	95	0	0
10	18	1	37	0	N	100	100	85	0	0
11	19	1	28	0	N	100	98	36	0	0
12	20	1	32	0	N	100	100	130	0	0
13	21	1	28	0	N	100	100	174	0	0
14	25	1	22	1	N	100	100	62	0	0
15	26	1	29	0	Y	100	98	99	0	0
16	27	1	27	1	N	100	100	120	0	0
17	28	1	29	0	N	100	100	91	0	0
18	35	1	32	1	Y	100	100	60	0	0
19	38	1	38	0	N	94	94	119	0	0
20	39	1	22	0	N	100	100	107	0	0
21	40	1	36	1	N	100	100	74	0	0
22	42	1	20	1	N	100	100	120	0	0
23	43	1	23	1	Y	100	100	86	0	0
24	45	1	35	0	N	100	100	65	0	0
25	46	1	32	1	N	100	100	110	0	0
26	47	1	25	1	Y	100	100	80	0	0
27	49	1	34	0	Y	100	100	181	0	0
28	50	1	24	0	Y	100	100	107	0	0
29	51	1	31	0	N	100	100	126	0	0
30	52	1	25	0	Y	100	100	79	0	0
31	53	1	25	1	Y	100	100	90	0	0

VILLAGE
1 = Mousharak Bahary. 3 = Kahk.
2 = Mousharak Qebly. 4 = Batn Ehrit.

Treat Code
Treatment Code.
1 = Niclosamide.
0 = Placebo.

Final Result
Y= Positive for S.heamatobium egg.
N= Negative for S.haematobium egg.

% Lotion Applica
% Lotion Application.

% Lotion Observa
% Lotion Observation.

Total Water Expos
total canal or irrigation water exposure.

Skin Comp
Skin complications.

Un-Prot Exposur
Unprotected canal or irrigation water exposure. i.e whole body exposure.

SERIAL NO.	SUBJECT ID.	VILLAGE	AGE	TREAT CODE	FINAL RESULT	%LOTION APPLICA	%LOTION OBSERVA	TOTAL WATER EXPOS	UN-PROT EXPOSUR	SKIN COMP
32	54	1	31	0	N	100	100	127	0	0
33	56	1	27	0	N	100	100	94	0	0
34	57	1	34	0	N	100	100	102	0	0
35	58	1	27	1	N	100	100	172	0	0
36	59	1	32	0	N	100	100	241	0	0
37	60	1	28	1	Y	100	100	96	0	0
38	62	1	22	1	N	100	100	136	0	0
39	64	1	18	0	Y	100	100	74	0	0
40	65	1	34	1	N	100	100	89	0	0
41	67	1	19	1	Y	100	100	124	0	0
42	68	1	38	0	Y	100	100	75	0	0
43	69	1	37	1	N	100	100	135	0	0
44	70	1	28	0	N	100	100	129	0	0
45	71	1	26	1	Y	100	100	130	0	0
46	72	1	22	1	Y	100	100	102	0	0
47	74	1	28	1	Y	100	100	149	0	0
48	75	1	25	0	N	100	100	133	0	0
49	76	1	31	0	N	100	100	140	0	0
50	77	1	18	1	N	100	100	89	0	0
51	78	1	19	0	N	100	100	119	0	0
52	80	1	27	0	N	100	100	216	0	0
53	83	1	39	1	Y	100	100	153	0	0
54	85	1	32	0	N	100	100	77	0	0
55	88	1	25	0	N	100	100	102	0	0
56	89	1	29	1	N	100	100	200	0	0
57	90	1	28	0	N	100	100	225	0	0
58	92	1	19	1	N	100	100	98	0	0
59	97	1	22	0	Y	100	100	40	0	0
60	99	1	25	0	N	100	100	192	0	0
61	100	1	34	1	N	100	100	202	0	0
62	101	1	18	0	N	100	100	202	0	0
63	102	1	20	1	Y	100	100	228	0	0
64	103	1	20	0	N	100	100	200	0	0
65	104	1	29	1	Y	100	100	205	0	0
66	106	1	18	1	Y	100	100	216	0	0
67	107	1	18	1	Y	100	100	237	0	0
68	109	1	20	0	Y	92	92	181	0	0
69	111	1	19	0	Y	100	100	118	0	0
70	112	1	28	0	N	94	94	99	0	0
71	114	1	28	0	Y	100	100	106	0	0
72	115	1	29	1	N	100	100	113	0	0
73	116	1	28	1	N	100	100	129	0	0
74	119	1	29	1	N	100	100	145	0	0
75	120	1	18	1	N	100	100	117	0	0
76	122	1	18	1	N	100	100	44	0	0
77	123	1	20	1	N	100	100	212	0	0
78	125	1	37	0	Y	100	100	42	0	0
79	126	1	36	1	N	100	100	90	0	0

SERIAL NO.	SUBJECT ID.	VILLAGE	AGE	TREAT CODE	FINAL RESULT	%LOTION APPLICA	%LOTION OBSERVA	TOTAL WATER EXPOS	UN-PROT EXPOSUR	SKIN COMP
80	130	1	27	1	Y	100	100	89	0	0
81	132	1	19	0	Y	100	100	65	0	0
82	134	1	25	0	N	100	100	82	0	0
83	138	1	26	1	N	100	100	98	0	0
84	142	1	39	1	Y	100	100	93	0	0
85	144	1	22	0	Y	100	100	103	0	0
86	145	1	23	1	Y	100	100	121	0	0
87	146	1	20	0	Y	100	100	115	0	0
88	147	1	20	1	N	100	100	202	0	0
89	148	1	22	1	N	100	100	30	0	0
90	150	1	25	0	Y	100	100	193	0	0
91	151	1	27	1	Y	100	100	115	0	0
92	157	1	27	1	N	100	100	124	0	0
93	158	1	19	1	N	94	94	105	0	0
94	161	2	25	0	N	100	100	62	0	0
95	162	2	29	1	N	100	100	94	0	0
96	166	2	29	0	Y	100	100	53	0	0
97	168	2	36	1	N	100	100	279	0	0
98	169	2	21	0	Y	100	100	91	0	0
99	170	2	38	0	N	100	100	55	0	0
100	172	2	32	0	N	100	100	84	0	0
101	175	2	24	1	Y	100	100	65	0	0
102	176	2	18	1	Y	100	100	58	0	0
103	177	2	32	0	Y	100	100	112	0	0
104	178	2	37	0	Y	92	92	108	0	0
105	179	2	24	1	N	100	100	44	0	0
106	181	2	19	0	Y	100	100	115	0	0
107	184	2	27	1	Y	100	100	111	0	0
108	187	2	39	1	N	100	100	94	0	0
109	188	2	33	0	Y	100	100	110	0	0
110	189	2	40	1	N	100	98	64	0	0
111	191	2	22	0	N	100	100	50	0	0
112	194	2	40	1	Y	100	100	60	0	0
113	197	2	32	1	Y	100	100	54	0	0
114	198	2	18	0	Y	100	100	67	0	0
115	200	2	29	0	Y	100	100	56	0	0
116	201	2	18	1	Y	100	100	54	1	0
117	203	2	31	0	N	100	100	62	0	0
118	204	2	22	0	N	100	100	130	0	0
119	205	2	28	0	N	100	100	107	0	0
120	206	2	21	1	N	100	100	53	0	0
121	207	2	22	1	N	100	100	84	0	0
122	208	2	38	0	N	100	100	53	0	0
123	209	2	18	0	N	100	100	34	0	0
124	210	2	23	0	N	100	100	211	0	0
125	213	2	27	0	N	100	100	329	0	0
126	218	2	38	1	N	100	100	120	0	0
127	219	2	33	0	N	100	100	99	0	0

SERIAL NO.	SUBJECT ID.	VILLAGE	AGE	TREAT CODE	FINAL RESULT	%LOTION APPLICA	%LOTION OBSERVA	TOTAL WATER EXPOS	UN-PROT EXPOSUR	SKIN COMP
128	221	2	18	0	N	100	100	124	0	0
129	222	2	18	1	N	100	100	98	0	0
130	223	2	26	1	N	98	98	189	0	0
131	225	2	19	1	Y	100	96	79	0	0
132	227	2	30	0	N	100	100	190	0	0
133	229	2	30	0	Y	100	100	125	0	0
134	230	2	32	1	Y	100	100	74	0	0
135	232	2	28	1	N	100	100	89	0	0
136	233	2	26	0	N	98	98	73	0	0
137	235	2	37	1	N	100	100	78	0	0
138	236	2	30	0	N	100	100	69	0	0
139	238	2	20	1	N	100	100	64	0	0
140	239	2	31	0	N	100	100	67	0	0
141	240	2	31	1	Y	100	100	78	0	0
142	241	2	29	0	N	100	100	152	0	0
143	243	2	35	1	Y	100	100	64	0	0
144	245	2	29	0	N	100	100	81	0	0
145	246	2	38	0	Y	100	100	70	0	0
146	247	2	26	1	N	100	100	78	0	0
147	248	2	34	1	Y	96	96	101	0	0
148	251	2	32	1	N	100	100	7	1	0
149	253	2	18	1	N	100	100	132	0	0
150	254	2	18	0	Y	100	100	30	2	0
151	256	2	20	1	N	100	98	39	0	0
152	257	2	19	0	N	100	100	62	0	0
153	258	2	37	0	N	100	94	172	0	0
154	265	2	36	0	N	100	86	166	0	0
155	266	2	20	1	N	100	90	104	0	0
156	267	2	23	1	N	100	90	138	0	0
157	268	2	28	0	N	100	88	65	0	0
158	269	2	40	1	N	100	86	56	0	0
159	271	2	27	1	N	98	80	29	0	0
160	273	2	28	0	N	92	92	73	0	0
161	274	2	38	0	Y	92	92	162	0	0
162	275	2	37	0	N	92	92	203	0	0
163	277	2	20	1	Y	92	92	95	0	0
164	279	2	33	1	Y	84	84	82	0	0
165	280	2	35	0	N	92	92	95	0	0
166	281	2	23	0	N	92	92	133	0	0
167	283	2	18	1	Y	92	92	97	0	0
168	284	2	18	1	Y	92	92	71	0	0
169	286	2	34	0	N	100	100	129	0	0
170	288	2	18	0	N	100	100	110	0	0
171	290	2	38	0	N	100	100	234	0	0
172	291	2	18	0	Y	100	100	97	0	0
173	292	2	26	1	Y	100	100	43	0	0
174	293	2	24	0	N	100	100	91	0	0
175	295	2	21	1	N	100	100	207	0	0

SERIAL NO.	SUBJECT ID.	VILLAGE	AGE	TREAT CODE	FINAL RESULT	%LOTION APPLICA	%LOTION OBSERVA	TOTAL WATER EXPOS	UN-PROT EXPOSUR	SKIN COMP
176	568	2	26	0	N	96	96	47	0	0
177	586	2	25	0	Y	88	88	98	0	0
178	587	2	32	1	N	96	88	91	0	0
179	593	2	29	1	N	96	96	55	0	0
180	594	2	39	0	N	96	96	50	0	0
181	596	2	18	0	Y	100	100	204	0	0
182	597	2	24	0	Y	100	100	134	0	0
183	598	2	19	0	N	100	100	72	0	0
184	296	3	24	0	N	100	75	65	0	3
185	298	3	37	0	N	100	78	47	0	0
186	299	3	37	0	N	100	75	33	0	0
187	303	3	35	0	N	100	57	92	0	0
188	305	3	34	0	N	100	94	92	0	1
189	307	3	29	1	N	98	98	88	0	0
190	309	3	19	0	N	100	94	109	0	0
191	310	3	33	1	N	100	96	48	0	0
192	314	3	22	1	N	100	100	28	0	0
193	315	3	37	1	N	100	100	120	0	0
194	317	3	26	0	N	100	100	169	0	0
195	318	3	37	1	N	100	100	56	0	0
196	321	3	39	0	Y	100	100	131	0	0
197	323	3	19	1	Y	100	100	164	0	0
198	325	3	38	1	N	100	100	85	0	0
199	328	3	21	0	N	100	100	120	0	0
200	333	3	21	0	N	100	100	24	0	0
201	335	3	22	1	N	100	100	149	0	0
202	336	3	18	0	Y	100	100	95	0	0
203	337	3	28	1	N	100	100	99	0	0
204	340	3	18	0	N	92	92	259	0	0
205	347	3	25	0	Y	100	100	104	0	0
206	348	3	35	1	Y	100	100	214	0	0
207	349	3	36	1	N	100	100	76	0	0
208	350	3	34	0	N	100	100	154	0	0
209	351	3	19	1	Y	100	100	118	0	0
210	352	3	39	1	N	100	100	140	0	0
211	353	3	37	1	N	100	100	118	0	0
212	354	3	32	1	N	100	100	143	0	0
213	355	3	21	0	N	100	100	144	0	0
214	357	3	30	0	N	100	100	181	0	0
215	358	3	34	0	N	100	100	239	0	0
216	359	3	28	0	N	100	100	97	0	0
217	364	3	38	1	N	100	100	168	0	0
218	365	3	18	0	N	100	100	88	0	1
219	367	3	37	1	N	100	98	110	0	0
220	368	3	28	1	Y	100	98	115	0	0
221	371	3	18	0	Y	100	96	119	0	0
222	372	3	18	0	N	100	100	54	0	0
223	373	3	38	0	Y	100	100	73	0	0

SERIAL NO.	SUBJECT ID.	VILLAGE	AGE	TREAT CODE	FINAL RESULT	%LOTION APPLICA	%LOTION OBSERVA	TOTAL WATER EXPOS	UN-PROT EXPOSUR	SKIN COMP
224	375	3	18	1	Y	100	100	52	0	0
225	376	3	31	1	Y	100	100	88	0	0
226	378	3	23	1	N	100	100	54	0	0
227	379	3	26	0	Y	100	100	80	0	0
228	380	3	28	1	Y	100	100	46	0	0
229	381	3	38	0	N	100	100	116	0	0
230	382	3	27	1	Y	100	100	77	0	0
231	383	3	19	1	N	100	100	71	0	0
232	385	3	37	1	Y	100	100	76	0	0
233	386	3	18	0	N	100	100	80	0	0
234	387	3	29	1	Y	100	100	60	0	0
235	388	3	30	0	N	100	100	103	0	0
236	393	3	30	0	Y	100	100	62	0	0
237	395	3	36	0	N	100	100	71	0	0
238	396	3	29	1	N	100	100	72	0	0
239	397	3	30	0	N	100	100	73	0	0
240	398	3	36	1	N	100	100	72	0	0
241	399	3	29	1	N	100	100	91	0	0
242	400	3	21	1	N	100	100	83	0	0
243	401	4	29	1	N	100	98	124	0	0
244	402	4	22	1	Y	100	100	103	0	0
245	405	4	36	1	Y	100	96	119	0	0
246	410	4	27	0	N	100	98	133	0	0
247	412	4	29	0	N	100	98	112	0	0
248	414	4	36	1	Y	100	98	211	0	0
249	415	4	23	0	N	100	98	146	0	0
250	418	4	32	1	N	100	98	202	0	0
251	422	4	29	1	N	98	92	80	0	0
252	423	4	36	1	Y	100	100	72	0	0
253	425	4	24	0	Y	76	76	56	0	0
254	426	4	20	1	N	100	100	59	0	0
255	427	4	32	1	N	100	100	92	0	0
256	428	4	39	0	N	100	100	67	0	0
257	429	4	28	0	N	88	86	110	0	0
258	431	4	25	0	N	100	100	74	0	0
259	432	4	27	1	N	100	100	89	0	0
260	433	4	27	0	N	100	98	104	1	0
261	436	4	18	0	N	100	98	53	0	0
262	438	4	37	0	N	98	98	57	0	0
263	439	4	19	0	Y	100	100	83	0	0
264	440	4	31	1	N	100	100	75	0	0
265	441	4	20	1	Y	100	100	55	2	0
266	442	4	26	0	N	100	100	63	2	0
267	443	4	40	0	N	100	100	74	2	0
268	444	4	28	0	Y	100	100	53	2	0
269	445	4	27	0	N	100	100	20	0	0
270	447	4	20	1	Y	100	100	50	0	0
271	448	4	18	1	N	100	100	57	0	0

SERIAL NO.	SUBJECT ID.	VILLAGE	AGE	TREAT CODE	FINAL RESULT	%LOTION APPLICA	%LOTION OBSERVA	TOTAL WATER EXPOS	UN-PROT EXPOSUR	SKIN COMP
272	449	4	40	1	N	100	100	67	1	0
273	450	4	40	1	Y	100	100	43	0	0
274	451	4	19	1	Y	100	100	75	0	0
275	452	4	38	0	N	100	98	173	0	0
276	453	4	18	0	N	100	100	72	0	0
277	456	4	39	0	Y	100	100	89	0	0
278	457	4	39	0	Y	92	92	72	0	0
279	461	4	36	0	N	100	100	66	0	0
280	462	4	19	1	N	100	100	77	0	0
281	463	4	20	1	N	100	100	88	1	0
282	464	4	35	1	N	100	100	126	0	0
283	465	4	33	0	N	100	100	127	0	0
284	466	4	29	0	Y	100	100	134	0	0
285	467	4	33	1	Y	100	100	147	0	0
286	468	4	18	1	N	94	94	105	0	0
287	472	4	38	1	Y	100	100	122	0	0
288	473	4	28	1	N	100	100	171	0	0
289	476	4	34	0	N	100	100	160	0	0
290	477	4	28	0	N	100	100	122	0	0
291	478	4	18	0	N	100	100	102	0	0
292	481	4	39	0	Y	100	100	112	0	0
293	484	4	39	0	Y	100	100	116	0	0
294	485	4	19	1	N	96	96	116	0	0
295	489	4	31	0	Y	100	100	108	0	0
296	490	4	24	1	N	100	100	126	1	0
297	491	4	39	1	N	100	100	249	0	0
298	493	4	25	0	N	100	100	167	1	0
299	498	4	31	0	N	100	100	161	0	0
300	500	4	22	0	Y	100	100	171	0	0
301	503	4	18	0	Y	100	100	152	0	0
302	504	4	19	0	Y	100	100	102	0	0
303	505	4	38	0	N	100	100	105	0	0
304	506	4	28	0	N	100	100	95	0	0
305	509	4	21	1	Y	100	100	100	0	0
306	510	4	28	0	Y	100	100	107	0	0
307	511	4	28	1	Y	100	100	110	0	0
308	512	4	35	1	N	100	100	98	0	0
309	514	4	20	1	N	100	100	115	0	0
310	516	4	22	0	Y	100	100	106	0	0
311	517	4	21	1	N	100	100	87	0	0
312	519	4	38	0	Y	100	100	84	0	0
313	520	4	22	0	Y	100	100	71	0	0
314	522	4	20	0	Y	100	100	77	0	0
315	523	4	35	0	Y	100	100	84	0	0
316	525	4	24	0	N	100	100	86	0	0
317	526	4	19	1	N	100	100	70	0	0
318	528	4	20	1	Y	100	100	75	0	0
319	529	4	33	0	N	100	100	88	0	0

SERIAL NO.	SUBJECT ID.	VILLAGE	AGE	TREAT CODE	FINAL RESULT	%LOTION APPLICA	%LOTION OBSERVA	TOTAL WATER EXPOS	UN-PROT EXPOSUR	SKIN COMP
320	530	4	18	0	N	100	100	53	0	0
321	531	4	19	1	N	100	100	40	0	0
322	532	4	39	0	N	100	100	119	0	0
323	536	4	18	1	N	100	100	92	0	0
324	537	4	22	1	N	100	100	109	0	0
325	538	4	31	1	N	92	92	34	0	0
326	541	4	19	0	N	94	92	69	0	0
327	545	4	35	1	N	100	98	137	0	0
328	548	4	37	1	N	100	88	97	1	0
329	550	4	20	0	N	100	100	116	0	0
330	551	4	20	1	N	100	100	104	0	0
331	552	4	19	0	N	100	100	50	0	0
332	553	4	39	0	Y	100	100	125	0	0
333	554	4	26	1	Y	100	100	108	0	0
334	556	4	21	0	N	100	100	154	0	0
335	559	4	18	1	N	100	100	61	0	0
336	560	4	38	0	N	98	96	80	0	0
337	563	4	20	1	Y	100	100	107	1	0
338	565	4	18	0	N	100	100	114	0	0
339	567	4	26	0	N	100	100	260	0	0
340	573	4	18	1	Y	100	100	139	0	0
341	574	4	37	0	N	100	100	69	0	0
342	576	4	40	1	N	100	100	76	0	0
343	577	4	24	1	N	100	100	70	0	0
344	578	4	24	1	N	100	100	78	0	0
345	580	4	24	1	Y	100	100	81	0	0
346	583	4	18	1	N	100	100	58	0	0
347	585	4	30	0	N	100	100	288	0	0
348	588	4	26	1	N	100	100	80	0	0
349	590	4	39	1	N	100	100	75	1	0
350	592	4	20	0	N	100	100	91	0	0

TABLE 5
Distribution Of Subjects By Study Villages

Musharak Bahary	Musharak Qebly	Kahk	Batn Ehrit	Total
93(26.6%)	90(25.7%)	59(16.9%)	108(30.9%)	350(100%)

TABLE 6

Distribution Of Subjects By Study Medication

Among The Four Villages

Study Medication	Musharak Bahary	Musharak Qebly	Kahk	Batn Ihrit	Total
Niclosamide	47(50.5%)	40(44.4%)	30(50.8%)	52(48.1%)	169(48.3%)
Placebo	46(49.5%)	50(55.6%)	29(49.2%)	56(51.9%)	181(51.7%)
Total	93(100%)	90(100%)	59(100%)	108(100%)	350(100%)

TABLE 7

Subject's Mean Age and Standard deviation In Years By Study Medication in The Four Villages

Study Medication	Musharak Bahary	Musharak Qebly	Kahk	Batn Ehrit	Total
Niclosamide	26.0± 6.3	27.3± 7.3	29.8± 6.8	26.6± 7.6	27.2± 7.1
Placebo	27.1± 5.8	28.0± 6.9	27.6± 7.5	28.3± 7.5	27.8± 6.9
Total	26.5± 6.0	27.7± 7.0	28.7± 7.2	27.5± 7.6	27.5± 7.0

TABLE 8

Lotion Application Compliance Among Study Groups In The Four Villages

% Lotion Application	Study Medication	Musharak Bahary n=93(100%)	Musharak Qebly n=90(100%)	Kahk n=59(100%)	Batn Ehrit n=108(100%)	Total n=350(100%)
98-100%	Niclosamide	46	33	30	49	158
	Placebo	43	41	28	52	164
	Total	89(95.7%)	74(82.2%)	58(98.3%)	101(93.5%)	322(92.0%)
90-97%	Niclosamide	1	6	0	3	10
	Placebo	3	8	1	2	14
	Total	4(4.3%)	14(15.6%)	1(1.7%)	5(4.6%)	24(6.9%)
< 90%	Niclosamide	0	1	0	0	1
	Placebo	0	1	0	2	3
	Total	0(0.0%)	2(2.2%)	0(0.0%)	2(1.9%)	4(1.1%)

TABLE 9

Lotion Application Observation By Study Monitors

Among Study Groups In The Four Villages

% Lotion Observation	Study Medication	Musharak Bahary n= 93(100%)	Musharak Qebly n= 90(100%)	Kahk n=59(100%)	Batn Ehrit n=108(100%)	Total n= 350(100%)
95-100%	Niclosamide	46	31	30	48	155
	Placebo	43	40	22	52	157
	Total	89(95.7%)	71(78.9%)	52(88.1%)	100(92.6%)	312(89.1%)
85-94%	Niclosamide	1	7	0	4	12
	Placebo	3	10	3	3	19
	Total	4(4.3%)	17(18.9%)	3(5.1%)	7(6.5%)	31(8.9%)
< 85%	Niclosamide	0	2	0	0	2
	Placebo	0	0	4	1	5
	Total	0(0.0%)	2(2.2%)	4(6.8%)	1(0.9%)	7(2.0%)

TABLE 10

Mean and Standard Deviation of infested water contact in hours reported during the entire study period by Study Medication in The Four Villages

Study Medication	Musharak Bahary	Musharak Qebly	Kahk	Batn Ehrit	Total
Niclosamide	122.9±49.5	86.8±49.2	96.0±42.4	98.1±42.1	101.9±47.7
Placebo	117.2±51.3	107.3±58.8	106.0±54.5	105.4±47.8	109.0±52.8
Total	120.1±50.2[a]	98.2±55.4[a]	100.9±48.6	101.9±45.1	105.6±50.4

[a] P = 0.05 Scheffe's multiple range test.

TABLE 11

Water contact Episodes involving non lotion-application areas reported by the study groups with the four villages

Unproctected water-contact Episodes	Study Medication	Musharak Bahary n=93(100%)	Musharak Qebly n=90(100%)	Kahk n=59(100%)	Batn Ehrit n=108(100%)	Total n=350(100%)
NONE	Niclosamide	47	38	30	45	160
	Placebo	46	49	29	51	175
	Total	93(100%)	87(96.7%)	59(100%)	96(88.9%)	335(95.7%)
ONE	Niclosamide	0	2	0	6	8
	Placebo	0	0	0	2	2
	Total	0(0.0%)	2(2.2%)	0(0.0%)	8(7.4%)	10(2.9%)
TWO	Niclosamide	0	0	0	1	1
	Placebo	0	1	0	3	4
	Total	0(0.0%)	1(1.1%)	0(0.0%)	4(3.7%)	5(1.4%)

TABLE 12

S. haematobium Reinfection Rates based on live and dead ova in urine up to 12 weeks after cessation of lotion application among study groups in The Four Villages

	Musharak Bahary			Musharak Qebly			Kahk			Batn Ehrit			Total		
	S.haematobium			S.haematobium			S.haematobium			S.haematobium			S.haematobium		
	+	-	R.R.*	+	-	R.R.	+	-	R.R.	+	-	R.R.	+	-	R.R.
Niclosamide	17	30	36.2%	12	28	30.0%	8	22	26.7%	15	37	28.8%	52	117	30.8%
Placebo	11	35	23.9%	16	34	32.0%	7	22	24.1%	17	39	30.4%	51	130	28.2%

* R.R. = Reinfection Rate.

TABLE 13

S. haematobium Reinfection Rates based on live and dead ova in urine up to 16 weeks after cessation of lotion application among study groups in The Four Villages

	Musharak Bahary			Musharak Qebly			Batn Kahk			Batn Ehrit			Total		
	S.haematobium			S.haematobium			S.haematobium			S.haematobium			S.haematobium		
	+	-	R.R.*	+	-	R.R.	+	-	R.R.	+	-	R.R.	+	-	R.R.
Niclosamide	20	27	42.6%	16	24	40.0%	10	20	33.3%	17	35	32.7%	63	106	37.3%
Placebo	16	30	34.8%	16	34	32.0%	7	22	31.8%	19	37	33.9%	58	123	32.0%

* R.R. = Reinfection Rate.

TABLE 14

S. haematobium Reinfection Rates based on live ova in urine up to 12 weeks after cessation of lotion application among study groups in The Four Villages

	Musharak Bahary			Musharak Qebly			Batn Kahk			Batn Ehrit			Total		
	S. haematobium			S. haematobium			S. haematobium			S. haematobium			S. haematobium		
	+	-	R.R.*	+	-	R.R.	+	-	R.R.	+	-	R.R.	+	-	R.R.
Niclosamide	6	41	12.8%	2	38	5.0%	4	26	13.3%	6	46	11.5%	18	151	10.7%
Placebo	6	40	13.0%	3	47	6.0%	4	25	13.8%	8	48	14.3%	21	160	11.6%

* R.R. = Reinfection Rate.

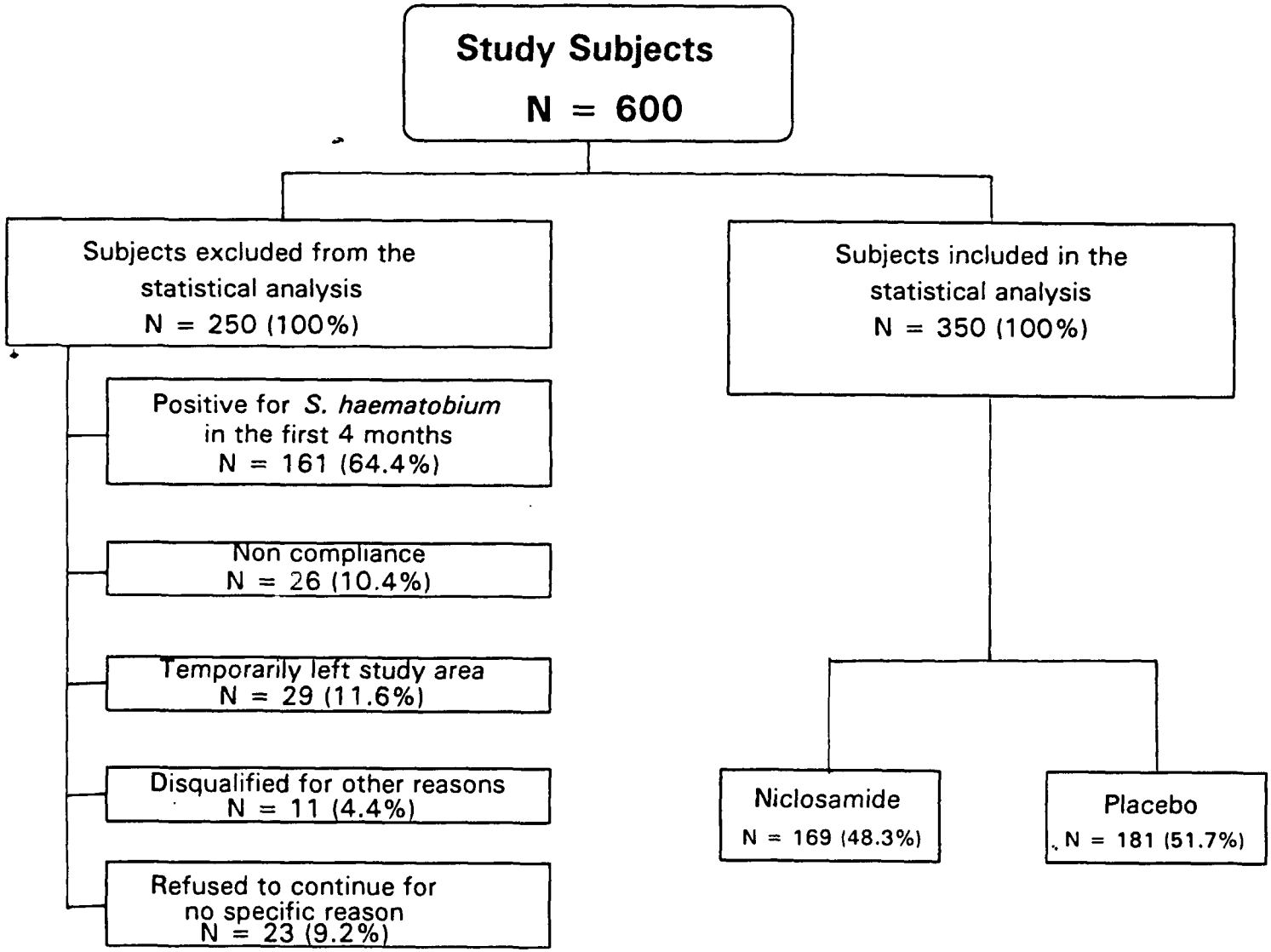
TABLE 15

S. haematobium Reinfection Rates based on live ova in urine up to 16 weeks after cessation of lotion application among study groups in The Four Villages

	Musharak Bahary			Musharak Qebly			Kahk			Batn Ehrit			Total		
	S.haematobium			S.haematobium			S.haematobium			S.haematobium			S.haematobium		
	+	-	R.R.*	+	-	R.R.	+	-	R.R.	+	-	R.R.	+	-	R.R.
Niclosamide	8	39	17.0%	5	35	12.5%	4	26	13.3%	7	45	13.5%	24	145	14.2%
Placebo	8	38	17.4%	3	47	6.0%	4	25	13.8%	10	46	17.9%	25	156	13.8%

* R.R. = Reinfection Rate.

FIGURE I. DESCRIPTION OF STUDY SUBJECTS



NSN 7540-00-834-4178

HEALTH RECORD

APPENDIX 1A

REPORT OF MEDICAL EXAMINATION

DATE

NORMAL	CLINICAL EVALUATION (Check each item in appropriate column, enter "NE" if not evaluated.)	ABNORMAL
	HEAD, FACE, NECK AND SCALP	
	NOSE	
	SINUSES	
	MOUTH AND THROAT	
	EARS - GENERAL (Int. and ext. canals) (Auditory acuity under items 70 and 71)	
	DRUMS (Perforation)	
	EYES - GENERAL (Visual acuity and refraction under items 59, 60 and 67)	
	OPHTHALMOSCOPIC	
	PUPILS (Equality and reaction)	
	OCULAR MOTILITY (Associated parallel movements, nystagmus)	
	LUNGS AND CHEST (Include breasts)	
	HEART (Thrust, size, rhythm, sounds)	
	VASCULAR SYSTEM (Varicosities, etc.)	
	ABDOMEN AND VISCERA (Include hernia)	
	ANUS AND RECTUM (Hemorrhoids, fistulae) (Prostate, if indicated)	
	ENDOCRINE SYSTEM	
	G-U SYSTEM	
	UPPER EXTREMITIES (Strength, range of motion)	
	FEET	
	LOWER EXTREMITIES (Except feet) (Strength, range of motion)	
	SPINE, OTHER MUSCULOSKELETAL	
	IDENTIFYING BODY MARKS, SCARS, TATTOOS	
	SKIN, LYMPHATICS	
	NEUROLOGIC (Equilibrium tests under item 72)	
	PSYCHIATRIC (Specify any personality deviation)	

NOTES (Describe every abnormality in detail. Enter pertinent item number before each comment. Continue in item 73 and use additional sheets if necessary.)

History of seizures Yes No

History of skin rash Yes No

History of allergy to Niclosamide or any other drug Yes No

History of any chronic medical problems Yes No

Date of last praziquantel treatment

Signature of examining physician Date

PATIENT'S IDENTIFICATION (Use this space for Mechanical Imprint)

RECORDS MAINTAINED AT:

PATIENT'S NAME (Last, First, Middle initial) | SEX

RELATIONSHIP TO SPONSOR | STATUS | RANK/GRADE

SPONSOR'S NAME | ORGANIZATION

DEPART./SERVICE | SSN/IDENTIFICATION NO. | DATE OF BIRTH

APPENDIX 1B

SN 7540-00-634-4178 600-108

HEALTH RECORD	CHRONOLOGICAL RECORD OF MEDICAL CARE
DATE	SYMPTOMS, DIAGNOSIS, TREATMENT, TREATING ORGANIZATION *(Sign each entry)*

PATIENT'S IDENTIFICATION *(Use this space for Mechanical Imprint)*

RECORDS MAINTAINED AT:

PATIENT'S NAME *(Last, First, Middle initial)*		SEX
RELATIONSHIP TO SPONSOR	STATUS	RANK/GRADE
SPONSOR'S NAME		ORGANIZATION
DEPART./SERVICE	SSN/IDENTIFICATION NO.	DATE OF BIRTH

CHRONOLOGICAL RECORD OF MEDICAL CARE **STANDARD FORM 600** (Rev. 6-84)
Prescribed by GSA and ICMR
FIRMR (41 CFR) 201-45.505

APPENDIX 2
DERMAL/SYSTEMIC REACTION RECORD

Name: _____
Subject Number: _____
Date Lotion Started: _____

	Date of Lesion	Date of Follow-up	Date of Follow-up	Date of Follow-up
Location of lesion				
Size of lesion				
Erythema formation:				
None				
Barely perceptible				
Well-defined				
Moderate to severe				
Severe (beet red)				
Edema formation:				
None				
Barely perceptible				
Slight (edges well-defined)				
Moderate (raised approx. 1.0 mm)				
Severe (raised beyond 1.0 mm)				
Other findings:				
Tender				
Weeping				
Abraded				
Generalized symptoms (describe)				
Signature of examiner, date, time				

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved OMB No. 0910-0230

FDA CONTROL NO

ACCESSION NO

I. REACTION INFORMATION

1 PATIENT ID/INITIALS *(In Confidence)*

2 AGE YRS

3 SEX

4-6 REACTION ONSET — MO | DA | YR

7 DESCRIBE REACTION(S)

13 RELEVANT TESTS/LABORATORY DATA

8-12 CHECK ALL APPROPRIATE:

- ☐ PATIENT DIED
- ☐ REACTION TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14 SUSPECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

15 DAILY DOSE

16 ROUTE OF ADMINISTRATION

17 INDICATION(S) FOR USE

18 DATES OF ADMINISTRATION *(From/To)*

19 DURATION OF ADMINISTRATION

20 DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA

21 DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22 CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

23 OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP, etc.)*

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24 NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*

24a IND/NDA NO. FOR SUSPECT DRUG

24b MFR CONTROL NO.

24c DATE RECEIVED BY MANUFACTURER

24d REPORT SOURCE *(Check all that apply)*
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25 5-DAY REPORT? ☐ YES ☐ NO

25a REPORT TYPE ☐ INITIAL ☐ FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26-26a NAME AND ADDRESS OF REPORTER *(Include Zip Code)*

26b TELEPHONE NO. *(Include area code)*

26c HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? ☐ YES ☐ NO

26d ARE YOU A HEALTH PROFESSIONAL? ☐ YES ☐ NO

Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction

NOTE: Required of manufacturers by 21 CFR 314.80

Appendix 4

Dates for Specimen Collection

	1st Sample	2nd Sample	3rd Sample
First Collection	9 May 92	10 May 92	11 May 92
Second Collection	6 Jun 92	7 Jun 92	8 Jun 92
Third Collection	4 Jul 92	5 Jul 92	6 Jul 92
Fourth Collection	1 Aug 92	2 Aug 92	3 Aug 92
Fifth Collection	12 Sep 92	13 Sep 92	14 Sep 92
Sixth Collection	10 Oct 92	11 Oct 92	12 Oct 92
Seventh Collection	7 Nov 92	8 Nov 92	9 Nov 92
Eighth Collection	5 Dec 92	6 Dec 92	7 Dec 92
Ninth Collection	2 Jan 93	3 Jan 93	4 Jan 93
Tenth Collection	30 Jan 93	31 Jan 93	1 Feb 93

APPENDIX 5

revised
15 November, 1992

NAMRU-3 SOP FOR THE DETECTION OF S. HAEMATOBIUM OVA IN URINE SPECIMENS

Description:

Schistosoma haematobium eggs are discharged into the urine of infected individuals. The urine specimen is best examined for the S. haematobium eggs by filtration followed by microscopic examination.

Collection:

1. Fresh urine is collected from patients in the morning in 50 ml plastic centrifuge tubes which are labeled by the field monitor with the subjects's name, study number, date, and village location.

2. The labeled specimens are delivered to the local village laboratory and sodium azide (.05 gm) is added to each specimen and mixed by shaking up and down several times within 6 hours of voiding.

3. The preserved urine specimens are transported to the NAMRU-3 laboratory in Cairo within 24 hours after the collection of the third consecutive daily specimen.

4. The specimens are logged in on the NAMRU-3 parasitology record forms and processed according to the prescribed procedure.

Method:

1. The urine specimens are mixed by inverting them up and down five times and then using the vortex for 30 sec. In case of urine specimens, which filled to the top of the tube, 5 ml of urine is discarded from the top of the tube in order that vortexing can be done.

2. Finally a 10 ml specimen is withdrawn by a 10 ml plastic disposable syringe connected to a 5 cm plastic extension tube having the same diameter as the needle adaptor from the middle of the specimen and then the plastic extension tube is removed and placed in a container with water and detergent.

3. The Nuclepore Pop-Top TM membrane holder (13 mm diameter) with the filter inside (Nuclepore, 13 mm diameter, 12.0 micron mesh size) on the support grid is connected on to the

syringe, then the 10 ml urine specimen is forced through the filter support containing the filter.

4. The syringe is disconnected form the filtration unit, filled with air and re-connected with the filter holder, twice, to expel excess urine and to force the eggs to adhere to the surface of the filter.

5. The filter is removed with blunt-tipped forceps and placed face down on the microscope slide. A drop of glycerine is used to fix the filter to the microscope slide and to improve visualization of the eggs under the 10 X objective with a binocular microscope. The same filtration assembly (with syringe) was used for the three samples of the same volunteer.

6. Each slide is examined microscopically by scanning each field in a systematic manner beginning at the upper left corner and moving the stage in parallel horizontal fields for at least four minutes.

7. The filter on the slide is kept and stored carefully in a horizontal slide box at room temperature for future reference.

Equipment:

1. Plastic disposable syringes, 10 ml

2. Plastic tube extension: 5 cm plastic tube extension with internal diameter of 3 mm.

3. Pop-Top TM membrane holder: Nuclepore, 13 mm diameter stock No. 420100

4. Nuclepore filters: 13 mm diameter, 12.0 micron mesh size, Qty: 100 Lot# 1555 No:110416

References:

Bradley, D.J. The measurement of bilharziasis prevalence and schistosomal egg output (aims and technique, with an account of a field method). Bulletin of the World Health Organization, 33: 503-508 (1965)

Bradley, D.J. Modified apparatus for parasitic filtration. Bulletin of the World Health Organization, 38: 828-832 (1968)

Peters, P.A., Warren, K.S. & Mahmoud, A.A.F. Rapid accurate quantification of schistosome eggs via Nuclepore filters. Journal of Parasitology, 62: 154-155 (1976)

Peters, P.A., Mahmoud, A.A.F., Warren, K.S., Ouma, J.H. & Arap Siongok, T.K. Field studies of rapid accurate means of quantifying Schistosoma haematobium eggs in urine samples. Bulletin of the World Health Organization, 54: 159-162 (1976)

APPENDIX 6
Laboratory Validation

The performance of the parasitology laboratory (NAMRU-3) was validated by inter-laboratory and intra-laboratory quality control (QC) programs.

I. Inter-laboratory QC program

1.a) NAMRU-3 laboratory received a monthly series of QC specimens from an outside reference laboratory: the Parasitology Department, Division of Experimental Therapeutics at Walter Reed Army Institute of Research (WRAIR). The QC specimens were urine specimens examined for *S. haematobium* eggs. The identification of the samples as negative or positive was not declared to anyone at NAMRU-3 until results were sent to WRAIR.

b) The initial five sets of specimens (forty, eighteen and ten thereafter)[3] were "openly" examined, i.e., the laboratory personnel (LP) were aware that they were analyzing QC specimens. However, the same procedure used to analyze the study participants specimens was followed.

c) The last four sets (ten, fifty and ten thereafter) were "blindly" examined: the QC coordinator inventoried and relabeled the QC specimens to appear as the study participants specimens (using I.D. numbers and names of participants who did not deliver specimens in those collections) and introduced the specimens among those of the study participants. Results of QC specimens were sent by Facsimile transmission followed by hard-copy reports to the TAP Project Officer at USAMMDA within three days of specimen examination. All specimens were saved until the results of the QC specimens were approved by the USAMMDA product manager.

d) The laboratory was required to correctly identify 90% of the specimens in each set. In two events, the 90% accuracy was not achieved and the NAMRU-3 laboratory took corrective measures agreed upon by the sponsor (USAMMDA product manager) and the principal investigator (NAMRU-3).

2. All mounted filtrates are saved in slide boxes, for possible re-examination.

II. Intra-laboratory QC program

1. For each collection, 10% of the mounted filtrates (~180) were examined twice. The QC coordinator did assign each LP (total of three) 30 each of the specimens he/she examined and those examined by another LP to re-examine. The assignment consisted of specimens with positive and negative results. In the first and sixth collections, 6% and 23% of the total number, respectively, were re-examined.

2.a) For collections #5-10, a positive pool for *S. haematobium* eggs in urine was prepared from the study participants specimens, verified, diluted when necessary with urine negative for *S. haematobium* eggs, aliquoted and introduced, with other specimens negative for *S. haematobium* eggs, among the specimens of the study participants (using I.D. numbers and names of participants who did not deliver specimens in those collections) to simulate specimens collected in the field.

INTER-LABORATORY QC PROGRAM
Report of Results. Set #1

Analyzed on: 3/15/1992

Sample #	Lab Result	Sample #	Lab Result
1	Negative	21	Positive
2	Positive	22	Negative
3	Negative	23	Negative
4	Negative	24	Negative
5	Negative	25	Positive
6	Positive	26	Negative
7	Positive	27	Positive
8	Negative	28	Positive
9	Negative	29	Positive
10	Negative	30	Positive
11	Negative	31	Negative
12	Negative	32	Negative
13	Positive	33	Negative
14	Negative	34	Negative
15	Negative	35	Positive
16	Negative	36	Positive
17	Negative	37	Positive
18	Positive	38	Negative
19	Positive	39	Positive
20	Positive	40	Negative

* Response from WRAIR:
  Total # correct: 36/40
  Negatives correctly identified: 19/19
  High positives (10-15 ova/10ml) correctly identified: 8/8
  Low positives (2-3 ova/10ml) correctly identified: 9/13
  (Misidentified specimens are #4, 11, 14 and 31)
* Accuracy: 90%
* Corrective action:
  Analyzing the remaining 40 ml for each of #4, 11, 14 and 31 as well as washing the containers five times with normal saline showed that the total number of eggs detected were 3, 6, 5 and 5 in the total volume of the four specimens, respectively.

INTER-LABORATORY QC PROGRAM
Report of Results. Set #2

* Analyzed on: 4/21/1992

Sample #	Lab Result	Sample #	Lab Result
41	Negative	50	Positive
42	Positive	51	Broken
43	Positive	52	Negative
44	Positive	53	Positive
45	Positive	54	Positive
46	Positive	55	Positive
47	Negative	56	Broken
48	Negative	57	Negative
49	Negative	58	Positive

* Response from WRAIR: All reported results are correct.

* Accuracy: 100%

INTER-LABORATORY QC PROGRAM
Report of Results. Set #3

* Analyzed on: 5/6/1992

Sample #	Lab Result	Sample #	Lab Result
59	Positive	64	Positive
60	Negative	65	Negative
61	Negative	66	Positive
62	Positive	67	Positive
63	Positive	68	Negative

* Response from WRAIR: All reported results are correct.

* Accuracy: 100%

INTER-LABORATORY QC PROGRAM
Report of Results. Set #4

* Analyzed on: 6/9/1992

Sample #	Lab Result	Sample #	Lab Result
69	Negative	74	Negative
70	Positive	75	Negative
71	Negative	76	Negative
72	Negative	77	Negative
73	Negative	78	Positive

* Response from WRAIR: All reported results are correct.

* Accuracy: 100%

INTER-LABORATORY QC PROGRAM
Report of Results. Set #5

* Analyzed on: 6/30/1992

Sample #	Lab Result	Sample #	Lab Result
79	Negative	84	Negative
80	Positive	85	Negative
81	Negative	86	Negative
82	Negative	87	Negative
83	Negative	88	Negative

* Response from WRAIR:
  Total # correct: 9/10
  Negatives correctly identified: 8/ 8
  Positives correctly identified: 1/ 2
  Low positives (3 ova/10ml) correctly identified: 1/2
  (# 82 is misidentified)

* Accuracy: 90%

* Corrective action:
  Analysis of the remaining 40 ml of sample #82 revealed the absence of *S. haematobium* eggs.

INTER-LABORATORY QC PROGRAM
Report of Results. Set #6

* Analyzed on: 8/16/92 - 8/19/92 with the specimens of the fourth (August) collection.

Sample #	Lab Result	Sample #	Lab Result
89	Negative	94	Negative
90	Negative	95	Negative
91	Negative	96	Negative
92	Negative	97	Negative
93	Negative	98	Negative

* Response from WRAIR:
  Total # correct: 7/10
  Negatives correctly identified: 7/7
  Positives correctly identified: 0/3
  (#90,95,96 are misidentified)

* Accuracy: 70%

* Corrective action:

1. Re-examination of the mounted filtrates (#90,95,96) revealed the absence of *S. haematobium* eggs.

2. Analysis of the remaining 40 ml of each specimen revealed the absence of *S. haematobium* eggs. However, analysis of rinsing fluid used to carefully wash the containers demonstrated one *S. haematobium* egg in #90.

3. Three sets of intra-laboratory QC specimens were investigated to achieve the ≥90% accuracy level (see below).

INTER-LABORATORY QC PROGRAM
Report of Results. Set #7

* Analyzed on: 9/17/92 - 9/28/92 with the specimens of the fifth (September) collection.

#	Result	#	Result	#	Result	#	Result
99	negative	112	negative	125	negative	138	negative
100	negative	113	negative	126	negative	139	negative
101	negative	114	negative	127	positive	140	negative
102	negative	115	positive	128	negative	141	negative
103	positive	116	negative	129	negative	142	negative
104	positive	117	negative	130	negative	143	negative
105	negative	118	positive	131	negative	144	negative
106	negative	119	negative	132	negative	145	negative
107	negative	120	negative	133	negative	146	negative
108	negative	121	negative	134	negative	147	negative
109	negative	122	negative	135	positive	148	positive
110	negative	123	negative	136	positive		
111	negative	124	negative	137	negative		

* Response from WRAIR:

Total # correct: 35/50
Negatives correctly identified: 28/29
Positives correctly identified: 7/21
Low positives (3 ova/10ml) correctly identified: 3/13
High positives (15 ova/10ml) correctly identified: 4/ 8
(#99, 101-102, 109, 112-114, 122, 128, 134, 136-137, 143, 145-146 are misidentified)

* Accuracy: 70% * Corrective action:

1. Re-examination of the mounted filtrates showed the same reported results.
2. Re-processing of the samples demonstrated the same reported results, but:
   a. #112 is positive; total # of ova detected is two
   b. #136 is negative, the previous reporting as positive could be explained by carry-over.
3. Re-processing of the samples (except #112) demonstrated the same reported results, but:
   a. #134 is positive; total # of ova detected is one
   b. #136 is negative, the previous reporting as positive could be explained by carry-over.
4. Three sets of intra-laboratory QC specimens were investigated to achieve the ≥90% accuracy level

INTER-LABORATORY QC PROGRAM
Report of Results. Set #8

* Analyzed on: 11/5/92 - 11/12/93 with the specimens of the sixth (October) collection.

* Result of the ten received specimens (#149-158): "Very Thick Can Not be examined (VTCNE)". The filtrates were re-examined and the specimens were re-processed with the same result "VTCNE".

INTER-LABORATORY QC PROGRAM
Report of Results. Set #9

* Analyzed on: 11/30/92 - 12/15/93 with the specimens of the seventh (November) collection.

#	Result	#	Result	#	Result	#	Result
159	N	162	N	165	N	168	VTCNE
160	VTCNE	163	VTCNE	166	VTCNE		
161	N	164	VTCNE	167	N		

* Response from WRAIR:
Total # correct: 3/10
Negatives correctly identified: 3/ 6
Positives correctly identified: 0/ 4
Low positives (3 ova/10ml) : 0/3 correct
High positives (15 ova/10ml): 0/1 correct
(# 161 and 167 were misidentified as negative beside the non-identified ones "VTCNE")

WRAIR-ET would try to determine if there had been some degradation in the pool of eggs. However, results of intra-laboratory QC program are encouraging.

INTRA-LABORATORY QC PROGRAM
Report of Results. May 92 (Collection #1)

The LP examined a total of 1746 specimens. Ninety-six mounted filtrates (5.5%) were re-examined. The reproducibility for the microscopic examination was 100%.

INTRA-LABORATORY QC PROGRAM
Report of Results. June 92 (Collection #2)

The LP examined a total of 1726 specimens. One-hundred and eighty mounted filtrates (10.4%) were re-examined. The reproducibility for the microscopic examination was 100%.

INTRA-LABORATORY QC PROGRAM
Report of Results. July 92 (Collection #3)

The LP examined a total of 1701 specimens. One-hundred and eighty mounted filtrates (10.6%) were re-examined. The reproducibility for the microscopic examination was 100%.

INTRA-LABORATORY QC PROGRAM
Report of Results. August 92 (Collection #4)

The LP examined a total of 1701 specimens. One-hundred and eighty mounted filtrates (10.6%) were re-examined. The reproducibility for the microscopic examination was 100%.

INTRA-LABORATORY QC PROGRAM
Report of Results. September 92 (Collection #5)

1. The LP examined a total of 1620 specimens. One-hundred and eighty mounted filtrates (11.1%) were re-examined. The reproducibility for the microscopic examination was 100%.

2. Three positive QC specimens were "blindly" examined among the specimens of the study participants and were correctly identified.

INTRA-LABORATORY QC PROGRAM
Report of Results of Corrective Actions
for the Inter-Laboratory QC specimens sets #6,7. October 92

In response to the discrepancies of results of the inter-laboratory QC specimens of sets #6,7 (analyzed with the 4th and 5th collections), the following measures were undertaken:

I) 1. Sixty QC specimens (37 negative, and 9 high positive, 2 intermediate positive and 12 low positive "15, 8-9 and 2-3 ova/10 ml, respectively") were prepared and "openly" processed.

2. Each of the three LP processed 20 specimens and examined the 60 filtrates.

3. Results were:

Total # correct:	49/60
Negatives correctly identified:	37/37
Positives correctly identified:	12/23
Low positives:	6/12 correct
Intermediate positives:	1/ 2 correct
High positives:	5/ 9 correct

* Accuracy: 81.7%

4. All the QC specimens with discrepant results were re-processed. *Results were as before except one specimen* which was correctly identified as positive.

5. All the intra-laboratory QC specimens with discrepant results were re-processed, but with the following modification in the procedure: "Specimens are mixed by inversion of the tube 5x then vortexing the tube 30 s". Results demonstrated that five of the eleven specimens were positive. Therefore,

Total # correct:	54/60
Negatives correctly identified:	37/37
Positives correctly identified:	17/23
Low positives:	8/12 correct
Intermediate positives:	1/ 2 correct
High positives:	8/ 9 correct

* Accuracy: 90%

II) 1. Twenty-four positive QC specimens (6 each of low, intermediate, high and very high positives containing 4, 8-9, 15-16 and 28-32 ova/10ml, respectively, were prepared.

2. Twelve specimens were "openly" processed, i.e. the LP knew that those were "positive" QC samples. The LP were required to perform egg count in the mounted filtrates. The processing (for 10 ml) was according to the S.O.P. but with the modification introduced in the sample mixing step. The other twelve specimens (a duplicate) were available for later evaluation by the Bell's technique, if deemed necessary.

3. Each of the three laboratory personnel processed 4 specimens representative of the different ova concentrations and examined the 12 filtrates.

4. Results showed that thirty-three of the thirty-six examinations (accuracy= 91.6%) were identified as containing *S. haematobium* ova. The identified count was equal to that of the expected range.

III) 1. Sixty QC specimens (36 negative, and 15 high positive, 6 intermediate positive and 3 low positive "15-32, 8-9 and 4 ova/10 ml, respectively") were prepared and "openly" processed as QC specimens.

2. Each of the three LP processed 20 specimens and examined the 60 filtrates.

3. Discrepancies were in four specimens. Therefore,

Total # correct:	56/60	
Negatives correctly identified:	36/36	
Positives correctly identified:	20/24	
Low positives:	2/ 3	correct
Intermediate positives:	6/ 6	correct
High positives:	12/15	correct

* Accuracy: 93.3%

INTRA-LABORATORY QC PROGRAM
Report of Results. October 92 (Collection #6)

1. The LP examined a total of 1580 specimens. Three-hundred and sixty mounted filtrates (22.8%) were re-examined. The reproducibility for the microscopic examination was 100%.

2.a) Fifty QC specimens (38 negative, and 6 high positive, 2 intermediate positive and 4 low positive "≥ 15, 8-9 and 3 ova/10 ml", respectively) were prepared and "blindly" processed among the specimens of the 6th collection.

2.b) The results were as expected except for four specimens (two each of negative and positive) which were reported as VTCNE. The mounted filtrates of the four specimens were re-examined with the same results. The four specimens were re-processed: one specimen was correctly identified as negative.

2.c) Therefore:

Total # correct:	47/50
Negatives correctly identified:	37/38
Positives correctly identified:	10/12
Low positives:	3/4 correct
Intermediate positives:	2/2 correct
High positives:	5/6 correct

* Accuracy: 94%

INTRA-LABORATORY QC PROGRAM
Report of Results. November 92 (Collection #7)

1. The LP examined a total of 1674 specimens. One-hundred and eighty mounted filtrates (10.7%) were re-examined. The reproducibility for the microscopic examination was 100%.

2.a) Fifty QC specimens (38 negative, and 6 high positive, 2 intermediate positive and 4 low positive "≥ 15, 8-9 and 3 ova/10 ml", respectively) were prepared and "blindly" processed among the specimens of the 7th collection.

2.b) The results were as expected except for a "negative" specimen which was reported as VTCNE.

* Accuracy: 98%

INTRA-LABORATORY QC PROGRAM
Report of Results. December 92 (Collection #8)

1. The LP examined a total of 1659 specimens. One-hundred and eighty mounted filtrates (10.9%) were re-examined. The reproducibility for the microscopic examination was 100%.

2.a) Fifty QC specimens (40 negative, and 6 high positive and 4 low positive "≥ 15 and 3 ova/10 ml", respectively) were prepared and "blindly" processed among the specimens of the 8th collection.

2.b) The results were as expected except for a "negative" specimen which was reported as positive, probably due to carry-over, being after a positive specimen in a set of three.

* Accuracy: 98%

INTRA-LABORATORY QC PROGRAM
Report of Results. January 93 (Collection #9)

1. The LP examined a total of 1677 specimens. One-hundred and eighty mounted filtrates (10.7%) were re-examined. The reproducibility for the microscopic examination was 100%.

2.a) Sixty QC specimens (45 negative, and 5 each of high, intermediate and low positive "≥15, 8-9 and 3 ova/10 ml", respectively) were prepared and "blindly" processed among the specimens of the 9th collection.

2.b) Results were as follows:

Total # correct:	56/60
Negatives correctly identified:	42/45
Positives correctly identified:	14/15
Low positives:	5/5 correct
Intermediate positives:	5/5 correct
High positives:	4/5 correct

The "positive" was reported as VTCNE. The three "negatives" were misidentified as positives probably due to carry over, as explained before.

* Accuracy: 93.3%

INTRA-LABORATORY QC PROGRAM
Report of Results. February 93 (Collection #10)

1. The LP examined a total of 1665 specimens. One-hundred and eighty mounted filtrates (10.8%) were re-examined. The reproducibility for the microscopic examination was 100%.

2.a) Sixty QC specimens (45 negative, and 5 each of high, intermediate and low positive "≥15, 8-9 and 3 ova/10 ml", respectively) were prepared and "blindly" processed among the specimens of the 10th collection.

2.b) Results were as expected with accuracy of 100%

APPENDIX 7a

CONSENT FORM

January 6, 1992

TITLE: A Placebo-controlled double blind study to determine the efficacy of a topically applied niclosamide 1% lotion in prevention of Schistosoma haematobium infection in Egyptian farmers

1. I _____ have been asked to participate in a medical research study being conducted by NAMRU-3 and the Egyption Ministry of Health Field Research Section on the prevention of schistosomiasis by means of a lotion applied two times per week to the arms, legs and torso to prevent schistosome penetration of skin. The experimental preparation is being used under the regulations of the U.S. Food and Drug Administration.

2. I understand that total avoidance of potentially schistosome infested fresh water is the best measure to avoid infection. Also the use of protective boots, gloves, and clothing would offer protection against infection. Fully aware of this information, I chose to work in water associated agriculture activities without water avoidance or protective measures as a matter of personal choice. I will participate in this study and apply a lotion to my arms, legs and torso as part of an evaluation of a new medication-lotion that may be effective in preventing infection.

3. I understand that voluntary participation is requested and if I agree to participate the following procedures will be conducted:
   a. An entry physical examination.
   b. Regular observations by study monitor of lotion application for 6 months and submission of 3 consecutive daily urine samples each month.
   c. Regular reporting of daily water contact to study monitor.
   d. Immediate reporting of any skin reactions or generalized responses to lotion.
   e. Follow-up for four months following lotion application with 3 consecutive urine specimens provided every month.
   f. Discontinuation of lotion and notification of monitor on the development of a skin reaction.
   g. Notification of study physician prior to taking any medications during the study period.

4. I understand that I will receive by chance, according to a number I am assigned, either niclosamide lotion or plain lotion without niclosamide, to be applied two times per week to my arms, legs and torso.

5. I understand that I will allow a study observer to show me how to apply the lotion and observe me apply it. I will apply the lotion as instructed. I will inform the study observer of the total amount of hours each day I am in contact with irrigation water.

6. I understand that some side effects may occur from the lotion such as a rash, itching, redness, or swelling. I agree to notify the physician within 24 hours after the occurrence of such skin reactions and will not use the lotion or contact irrigation water until my skin is clear and I am given permission from the study physician.

7. I understand that NAMRU-3 will provide the necessary health care for medical problems resulting from treatment with lotion including general reactions and skin reactions.

8. I understand that my participation in this study is voluntary and I may withdraw at any time. I will if I desire have a urine evaluation at the end of the study or whenever I chose to withdraw and be provided schistosomal treatment medication if infection is detected.

9. I understand that this study may be of no direct benefit to me since there is no evidence the plain lotion or 1% niclosamide will prevent schistosomiasis. I will obtain free diagnosis and treatment for schistosomiasis infection.

10. I understand that medical information obtained during my participation in this study will be kept confidential and reported without revealing my identity only in a scientific publication or presentation. Representatives of the Egyptian Ministry of Health, U.S. Food and Drug Administration and U.S. Army may inspect records of this study.

11. I understand that I may contact DR. Remon or Dr. Magid (Ipshway District Health Officer) for the information about the research. Additionally, I may contact the chairman of the committee for the protection of Human Subjects at NAMRU-3 (Dr. Gray, telephone #(02)284-1375 (Cairo) for the information about research subject's rights.

12. I understand that I will receive a copy of this consent from.

_____ _____

Participant's Name Date

_____

Participant's Address

_____

Participant's signature

_____ _____

Witness's Name Witness's Signature

APPENDIX 7b

اقرار بالموافقة

عنوان الدراسة : دراسة لمقارنة الدهان الموضعي الذي يحتوي على ١٪ نيكلوساميد بدهان مشابه في جميع مكوناته عدا المادة الفعالة للوقاية من البلهارسيا البولية التي تصيب الفلاحين المصريين.

١- قد طلب مني أنا _____ الإشتراك في الدراسة الطبية التي تجريها الناصر-٣ والإدارة العامة لمكافحة البلهارسيا بوزارة الصحة للوقاية من البلهارسيا باستخدام كريم يوضع مرتين أسبوعيا على الذراعين والساقين والجسم ليمنع اختراق سركاريا البلهارسيا للجلد. وقد استخدم المركب التجريبي طبقا للوائح الخاصة لهيئة الأغذية والعقاقير الأمريكية و سوف يستخدم تحت الإشراف الطبي للدكتور/ جون بودجون و الدكتور/ ريمون أبو الزيد.

٢- أنا أعلم أن أفضل و سيلة لتجنب الإصابة بالمرض هي التجنب التام للمياة العذبة الموبوءة بالبلهارسيا. كما أن استخدام الأحذية الواقية (البوت)، القفازات و الملابس الواقية توفر الحماية من هذا المرض و مع علمي تماما بكل ذلك فقد اخترت بنفسي العمل في هذة المياة التي تستخدم في الزراعة بدون استخدام وسائل للوقاية. و سوف اشترك في الدراسة وسامح الكريم على الذراعين والساقين والجسم مرتين في الأسبوع وذلك لتقييم الدهان الواقي الجديد الذي ربما يكون فعالا في منع الإصابة بالمرض.

٣- أنا أعلم هذة الدراسة تتطلب اشتراكي التطوعي واذا وافقت على الإشتراك في الدراسة فسوف يجري لي الآتي :-

ا - فحص طبي عند بداية الإشتراك في الدراسة.
ب - ملاحظة مستمرة بواسطة مراقب الدراسة على الدهان الموضعي لمدة ستة أشهر.
ج - ابلاغ مراقب الدراسة بانتظام بمدى تعرضي اليومي للمياة.
د - و ابلاغه فورا عن أي التهابات جلدية أو عامة نتيجة استخدام الدهان.
هـ- المتابعة لمدة اربعة أشهر تالية لإستخدام الدهان مع اعطاء عينات بول كل شهر.
و - ايقاف استخدام الدهان و ابلاغ مراقب الدراسة عن وجود تطور أي التهاب جلدي.
ز - ابلاغ طبيب الدراسة قبل تناول أي عقاقير خلال فترة الدراسة.

٤- أنا أعلم أنني سوف اتلقى عشوائيا، طبقا لرقمي، اما دهان بة نيكلوساميد أو دهان ليس بة نيكلوساميد ليوضع مرتين أسبوعيا على الذراعين ، الساقين ، و الجسم.

٥- أنا أعلم أنني سأسمح لأحد ملاحظي الدراسة أن يريني كيفية استخدام الدهان و أن يراقبني أثناء وضعة . و سأستخدم الدهان حسب التعليمات. أيضا سوف أعطي ملاحظ الدراسة عينة بول يوميا لمدة ثلاث أيام متتالية من كل شهر و لمدة تسعة أشهر أيضا سوف أبلغ ملاحظ الدراسة بعدد الساعات التي أتعرض فيها لمياة الري يوميا

٦- أنا أعلم أنة ممكن حدوث بعض الأعراض الجانبية عند استخدام الدهان مثل الطفح الجلدي، هرش، احمرار، او ورم. وأوافق على أبلاغ مراقب الدراسة في أقرب وقت عند حدوث مثل هذة الإلتهابات الجلدية و لن أستعمل الدهان و لن أتعرض لمياة الري حتى يصبح جلدي سليما و يصرح لي بواسطة طبيب الدراسة.

٧- أنا أعلم أن النامرو-٣ سوف تقدم الرعاية الصحية الضرورية للأعراض المرضية التي قد تنشأ من استخدام الدهان سواء كانت جلدية أو عامة.

٨- أنا أعلم أن اشتراكي في الدراسة بإرادتي ويمكنني الانسحاب منها في أي وقت و لي الحق في طلب فحص عينات دم عند نهاية الدراسة أو عند الانسحاب من الدراسة و أن يقدم لي العلاج اذا كنت مصابا بالبلهارسيا.

٩- أنا أعلم أنني لن استفيد مباشرة من هذه الدراسة لأنة لا يوجد دليل على أن الدهان الغير فعال أي الذي به ١ ٪ نيكلوسامايد سوف يمنع الاصابة بالبلهارسيا. و سوف أحصل على تشخيص و علاج مجاني لمرض البلهارسيا.

١٠- أنا أعلم أن المعلومات الطبية التي تحصلون عليها أثناء اشتراكي في البحث سوف تبقى سرية و سيتم نشرها بدون الكشف عن شخصيتي في أي نشرة علمية أو مؤتمر علمي. و يمكن لممثلي وزارة الصحة المصرية، و الادارة الاعدية و العاقير الأمريكية فحص هذة السجلات.

١١- أنا أعلم أنة يمكنني الاتصال بالدكتور / ريمون أي الدكتور / ماجد (مدير الادارة الصحية بأبشواي) لطلب معلومات عن هذا البحث. بالاضافة الى ذلك يمكنني الاتصال برئيس لجنة حماية حقوق استخدام الانسان في البحث بالنامرو-٣ (د. جراي) تليفون (٠٢-٢٨٤١٣٧٥) بالقاهرة لمعرفة معلومات أكثر عن حقوق المشتركين في البحث.

١٢- أنا أعلم أنني سأستلم نسخة من هذا الاقرار.

_____

اسم المشترك

_____ / / ١٩

توقيع المشترك التاريخ

_____

عنوان المشترك

_____

اسم الشاهد

_____ / / ١٩

توقيع الشاهد التاريخ

APPENDIX 8a

Daily Log Book

Participant Name _____ ID No. _____

Village _____ _____/_____ Week No. _____/_____

Date	___/___	___/___/___
Time of visit	_____	_____
Lotion Application	Yes[ ] No[ ]	Yes[ ] No[]
Lotion Observation	Yes[ ] No[ ]	Yes[ ] No[]
Presence of skin reaction	Yes[ ] No[ ]	Yes[ ] No[]
No of empty vials	_____	_____
Since last visit:		
1. Time spent in canal or irrigation water	_____	_____
2. No of ablution using canal water	_____	_____
3. Unprotected water exposure in canal/ irrigation water	Yes[ ] No[ ]	Yes[ ] No[]
If the answer is Yes explain	_____	_____
	_____	_____

Date	___/___/___	___/___/___
Time of visit	_____	_____
Lotion Application	Yes[ ] No[ ]	Yes[ ] No[]
Lotion Observation	Yes[ ] No[ ]	Yes[ ] No[]
Presence of skin reaction	Yes[ ] No[ ]	Yes[ ] No[]
No of empty vials	_____	_____
Since last visit:		
1. Time spent in canal or irrigation water	_____	_____
2. No of ablution using canal water	_____	_____
3. Unprotected water exposure in canal/ irrigation water	Yes[ ] No[ ]	Yes[ ] No[]
If the answer is Yes explain	_____	_____
	_____	_____

Monitor's Name_____ Signature_____

APPENDIX 8b

نموذج التسجيل اليومي

الاسم : _____ الرقم : _____

اسم القرية : _____ رقم الاسبوع : ___ / ___

التاريخ : ___ / ___ / ___ التاريخ : ___ / ___ / ___

وقت الزيارة : _____ وقت الزيارة : _____

هل تم الدهان بالكريم	نعم	لا	هل تم الدهان بالكريم	نعم	لا
مساعدة الدهان بالكريم	نعم	لا	مساعدة الدهان بالكريم	نعم	لا
وجود مهاعفات جلدية	نعم	لا	وجود مهاعفات جلدية	نعم	لا
عدد العبوات الفارغة	_____		عدد العبوات الفارغة	_____	

منذ الزيارة السابقة :
١- الوقت الذي قضى في الري أو مياه الترعة _____
٢- عدد مرات الوضوء في مياه الترعة _____
٣- التعرض لمياه الري أو الترعة أكثر من الاجزاء المدهونة نعم لا
اذا كانت الاجابة بنعم وضح _____

منذ الزيارة السابقة :
١- الوقت الذي قضى في الري أو مياه الترعة _____
٢- عدد مرات الوضوء في مياه الترعة _____
٣- التعرض لمياه الري أو الترعة أكثر من الاجزاء المدهونة نعم لا
اذا كانت الاجابة بنعم وضح _____

التاريخ : ___ / ___ / ___ التاريخ : ___ / ___ / ___

وقت الزيارة : _____ وقت الزيارة : _____

هل تم الدهان بالكريم	نعم	لا	هل تم الدهان بالكريم	نعم	لا
مساعدة الدهان بالكريم	نعم	لا	مساعدة الدهان بالكريم	نعم	لا
وجود مهاعفات جلدية	نعم	لا	وجود مهاعفات جلدية	نعم	لا
عدد العبوات الفارغة	_____		عدد العبوات الفارغة	_____	

منذ الزيارة السابقة :
١- الوقت الذي قضى في الري أو مياه الترعة _____
٢- عدد مرات الوضوء في مياه الترعة _____
٣- التعرض لمياه الري أو الترعة أكثر من الاجزاء المدهونة نعم لا
اذا كانت الاجابة بنعم وضح _____

منذ الزيارة السابقة :
١- الوقت الذي قضى في الري أو مياه الترعة _____
٢- عدد مرات الوضوء في مياه الترعة _____
٣- التعرض لمياه الري أو الترعة أكثر من الاجزاء المدهونة نعم لا
اذا كانت الاجابة بنعم وضح _____

اسم الملاحظ _____ توقيعة _____